ORPHAN DRUGS TO BE FOLLOWED

Identifying and characterizing the development of follow-on Orphan Medicinal Products in Europe

(copied from Swedish Orphan International, 2010)

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Master thesis

Steering Committee on Orphan Drugs
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CONTENTS

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Since the first year of my study Science and Innovation Management, I was interested in the orphan drug field and it was obvious for me that I wanted to do research within this field. This master thesis gave me the opportunity to do that research. However, without the great support of several persons, this research was never completed in such a way it is now.

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Anne Brabers
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SUMMARY

Rare diseases are diseases which have a low prevalence and are mostly life-threatening or seriously debilitating. It is estimated that more than 55 million people in Europe and the United States of America together are affected by one of the 5,000 to 8,000 different known rare indications. For many of these rare diseases no adequate treatments have come available. This lack of adequate treatments is explained by the fact that orphan drugs are unsuccessful pharmaceutical innovations due to the low estimated economic profitability. Sponsors are therefore not interested in developing a treatment for these diseases. Finding effective and safe treatments for patients suffering from rare diseases is therefore an important public health issue. Consequently, and to encourage pharmaceutical innovations for orphan diseases, different orphan legislations were implemented.

Despite these orphan legislations, for many rare diseases no effective and safe treatments are available yet. At the same time, some orphan diseases are associated with a high number of orphan medicinal products (OMP's). More detailed, for some rare indications with an authorized OMP on the market, other follow-on OMP's (FOMP's) are in development or sometimes even authorized. This implies a (skewed) distribution for orphan drug development and more specific, for FOMP development. As a result, part of the patients suffering from an orphan disease never get access to better, and finally optimal, treatments for their rare disease, despite the fact that the legislations were aimed at giving patients of rare diseases access to treatments having the same quality as other patients. This thesis therefore aimed to elucidate this (skewed) distribution. On the one hand, this thesis aimed to identify the factors explaining FOMP development and, on the other hand, to characterize the sponsors of FOMP's in development. This resulted in the following main research question to be answered within this thesis: **which factors explain the development of FOMP's and how can the sponsors of FOMP's be characterized?**

Van Noordwijk (1984) identified three prerequisites complying to a successful pharmaceutical innovation, namely economic profitability, technological feasibility and medical need. More detailed, this framework gives insight in a diverse range of aspects involved in drug development and was therefore used in this thesis to examine factors explaining the development of FOMP's. However, this thesis adapted the prerequisites of Van Noordwijk (1984) to get broader characteristics that better fit to orphan drug development. As a result, this thesis investigated the following characteristics: product-related (technological feasibility), market-related (economic profitability) and disease-related (medical need) characteristics. A comparison between rare indications with an approved OMP and at least one FOMP and rare indications with an approved OMP and no FOMP was performed to identify possible factors explaining FOMP development. Thereafter, the characterization of the sponsors of FOMP's was examined by describing some business-related characteristics of the sponsors and by describing to what extent, and for what reason, sponsors of FOMP's are characterized by a positive decision to continue further development after market authorization of the first OMP for a particular rare disease. As a matter of fact, sponsors of FOMP's are not able to fully benefit from the main innovation encouraging market exclusivity instrument. In addition, the concept of significant benefit was used to investigate the reason for the decision of FOMP sponsors, since FOMP sponsors have to show significant benefit to obtain a market approval. This thesis performed descriptive statistics for the characterization of FOMP sponsors. Finally, all data in this thesis was collected from sources in the public domain only. Moreover, this thesis was mainly focused on Europe, however, some additional analyses were done for an US sample.

The development of at least one FOMP was strongly associated with the disease prevalence (market size) of the rare indication (odds ratio: 25.2; confidence interval: 2.5-259.2). In addition, from the US sample the disease class (oncology) was observed as second predictor for FOMP development. FOMP sponsors, and especially authorized FOMP sponsors, were characterized by a high percentage (46.4 %) of large-sized firms. Furthermore, most (53.3 %) FOMP sponsors had at least two other orphan designations (OD's). In addition, all sponsors – except for one – decided to continue further development after market authorization of the first OMP for the same rare indication. Moreover, this thesis observed that termination of FOMP development was mostly related to conducting clinical trials, focus on another more promising indication of the same OMP, registration failure and the lack of funding. Finally, the findings showed that almost all (93.3 %) FOMP sponsors expect to demonstrate an improved efficacy compared to the first approved OMP for the same rare indication.

This thesis showed that the market size (disease prevalence) of a rare indication is an important predictor for the development of at least one FOMP for rare diseases with an authorized OMP. In addition, in the US sample, the disease class was found as second predictor for the development of at least one FOMP for rare indications with an authorized OMP. FOMP sponsors, and even more the sponsors of authorized FOMP's, are characterized by a high percentage of experienced and large-sized firms. Further characterization of FOMP development reveals a strong preference by large-sized sponsors for orphan drug development for rare diseases having a prevalence above 1 per 100,000 and oncologic disorders. Finally, the sponsors appear to be satisfied with a shared market exclusivity due to their positive decision regarding further development after market approval of the first OMP for the same rare indication. As a result, the instrument of market exclusivity does *not* create a disincentive for other companies to invest in rare diseases having an approved OMP. More general, from our results it is concluded that an instrument, aimed at encouraging pharma innovation for unmet medical needs, does *not* contribute to the lock-in of one particularly technology (i.e. an authorized OMP). In addition, almost all of the FOMP sponsors expect to justify significant benefit by showing an improved efficacy profile compared to the first approved OMP.

The aim of this research was to further elucidate the observed (skewed) distribution of OMP's. It is concluded that there is a skewed distribution for the translation of rare disease research into the start of an orphan drug program, for approved OMP's and even for FOMP development. The current legislation is thus not sufficient to give all the patients suffering from orphan diseases access to treatments with the same quality as other patients. As a result, to address the found skewed distribution, additional (financial) incentives have to be implemented to encourage drug development for rare diseases having a prevalence below 1/100,000. In addition, the involved large-sized firms in FOMP development often have obtained the necessary experience to bring the FOMP to the market, however, also the FOMP's owned by SME's should be able to obtain market authorization. To address the skewed distribution it is thus also important to focus on SME's. The EMA addresses this issue by giving sponsors scientific advice and protocol assistance and by having launched a SME office dedicated to the (regulatory) needs of the SME's. Based on the results of this thesis, new policy measures regarding stimulating pharma innovation by means of regulation have to take into account the following two issues, i.e. equally addressing the unmet medical needs and focusing on inexperienced companies (mostly SME's) to give them also the possibility to fully benefit from the provided incentives of the regulation.

SAMENVATTING

Zeldzame ziekten zijn ziekten die een lage prevalentie hebben en meestal levensbedreigend of ernstig invaliderend zijn. Er wordt geschat dat in totaal meer dan 55 miljoen mensen in Europa en de Verenigde Staten van Amerika lijden aan een van de 5.000 tot 8.000 verschillende zeldzame ziekten. Voor veel van deze zeldzame indicaties zijn geen geschikte behandelingen beschikbaar. Het ontbreken van adequate behandelingen kan worden verklaard uit het feit dat weesgeneesmiddelen onsuccesvolle farmaceutische innovaties zijn ten gevolge van een laag geschatte economische winstgevendheid. Sponsors zijn daarom niet geïnteresseerd in de ontwikkeling van een behandeling voor deze ziekten. Het vinden van effectieve en veilige behandelingen voor patiënten die lijden aan een zeldzame indicatie is daarom een belangrijk onderwerp voor de volksgezondheid. Als gevolg hiervan, en om farmaceutische innovaties voor zeldzame indicaties te stimuleren, zijn verschillende wetgevingen geïmplementeerd.

Ondanks deze wetgevingen zijn voor veel zeldzame ziekten geen effectieve en veilige behandelingen beschikbaar. Tegelijkertijd worden sommige zeldzame ziekten geassocieerd met een hoog aantal 'orphan medicinal products' (OMP's). Meer specifiek, voor bepaalde zeldzame ziekten met een goedgekeurde OMP beschikbaar, zijn andere 'follow-on' OMP's (FOMP's) in ontwikkeling of zelfs goedgekeurd. Dit impliceert een (scheve) verdeling voor de ontwikkeling van weesgeneesmiddelen en meer gedetailleerd, voor FOMP ontwikkeling. Als gevolg hiervan krijgt een deel van de patiënten die lijden aan een weesziekte nooit toegang tot betere, of optimale, behandelingen, ondanks het feit dat de wetgevingen er op gericht zijn patiënten met een zeldzame indicatie toegang te geven tot behandelingen met dezelfde kwaliteit als andere patiënten. Deze thesis had dus als doel deze (scheve) verdeling toe te lichten. Aan de ene kant, had deze thesis als doel om de factoren die de ontwikkeling van FOMP's verklaren te identificeren, en aan de andere kant, om de sponsors van FOMP's in ontwikkeling te karakteriseren. Dit leidde tot de volgende onderzoeksvraag die werd beantwoord in deze thesis: **welke factoren verklaren de ontwikkeling van FOMP's en hoe kunnen de sponsors van FOMP's worden gekarakteriseerd?**

Van Noordwijk (1984) identificeerde drie voorwaarden waaraan een succesvolle farmaceutische innovatie moet voldoen: economische winstgevendheid, technologische haalbaarheid en medische behoefte. Meer specifiek geeft dit kader inzicht in een breed scala aan aspecten die betrokken zijn bij de ontwikkeling van geneesmiddelen. Als gevolg hiervan werd dit kader in deze thesis gebruikt om factoren die de ontwikkeling van FOMP's verklaren te onderzoeken. Deze thesis paste echter de voorwaarden van Van Noordwijk (1984) aan om op deze manier bredere karakteristieken te krijgen die beter aansluiten bij weesgeneesmiddelen. Deze thesis onderzocht als gevolg hiervan de volgende karakteristieken: productgerelateerde (technologische haalbaarheid), marktgerelateerde (economische winstgevendheid) en ziektegerelateerde (medische behoefte) karakteristieken. Een vergelijking tussen zeldzame ziekten met een goedgekeurde OMP en tenminste één FOMP en zeldzame ziekten met een goedgekeurde OMP en geen FOMP werd uitgevoerd om zo de mogelijke factoren die FOMP ontwikkeling verklaren te identificeren. De karakterisering van de sponsors van FOMP's is daarna onderzocht door het beschrijven van bedrijfsgerelateerde kenmerken van de sponsors en door het beschrijven van in welke mate, en om welke reden, sponsors van FOMP's een positief besluit nemen ten aanzien van continuering van ontwikkeling van hun FOMP na markt goedkeuring van de eerste OMP voor een specifieke weesziekte. In feite zijn FOMP sponsors namelijk niet in staat om volledig te profiteren van het belangrijkste innovatie stimulerende markt exclusiviteit instrument. Het concept 'significant benefit' (aanzienlijk voordeel) werd gebruikt om de reden voor de beslissing van FOMP sponsors te onderzoeken,

aangezien FOMP sponsors een aanzienlijk voordeel moeten aan tonen om markt goedkeuring te verkrijgen. Deze thesis voerde beschrijvende statistieken uit voor de karakterisering van FOMP sponsors. Tot slot wordt opgemerkt dat de data in deze thesis alleen werd verzameld uit bronnen in het publieke domein. Daarnaast is in deze thesis vooral gefocust op Europa, echter, een aantal additionele analyses voor een US steekproef zijn gedaan.

De beschikbaarheid van tenminste één FOMP was sterk geassocieerd met de grootte van de markt (dwz. ziekte prevalentie) van de weesziekte (odds ratio: 25,2; betrouwbaarheidsinterval: 2,5-259,2). Daarnaast bleek, uit de US steekproef, de ziekte klasse (oncologie) een tweede voorspeller met betrekking tot FOMP ontwikkeling. FOMP sponsors, en vooral de goedgekeurde FOMP sponsors, waren gekenmerkt door een hoog percentage (46,4 %) van grote bedrijven. Verder hadden de meeste (53,3 %) FOMP sponsors op zijn minst twee andere producten met een weesgeneesmiddelstatus. Ook besloten alle sponsors – met uitzondering van één – ontwikkeling van hun FOMP voort te zetten na de markt goedkeuring van de eerste OMP voor dezelfde zeldzame ziekte. Uit deze thesis bleek eveneens dat beëindiging van ontwikkeling van een FOMP met name was gerelateerd aan het doen van klinische studies, focus op een andere meer belovende indicatie van dezelfde OMP, falen tijdens de registratie procedure en het gebrek aan financiering. De resultaten toonden tenslotte aan dat bijna alle (93,3 %) sponsors verwachten een verbeterde effectiviteit aan te tonen in vergelijking met de eerste goedgekeurde OMP voor dezelfde weesziekte.

Deze thesis toonde aan dat de markt grootte (dwz. ziekte prevalentie) van een zeldzame indicatie een belangrijke voorspeller is voor de ontwikkeling van minstens één FOMP voor weesziekten met een goedgekeurde OMP. In de US steekproef is daarnaast de ziekte klasse als tweede voorspeller gevonden voor de ontwikkeling van minstens één FOMP voor weesziekten met een goedgekeurde OMP. FOMP sponsors, en vooral sponsors van goedgekeurde FOMP's, zijn gekenmerkt door de betrokkenheid van een hoog percentage van ervaren en grote sponsors. Verdere karakterisering toonde een sterke voorkeur van grote sponsors voor weesgeneesmiddel ontwikkeling voor ziekten met een prevalentie hoger dan 1/100,000 en oncologische aandoeningen. Tot slot lijken de sponsors van FOMP's tevreden te zijn met gedeelde markt exclusiviteit als gevolg van hun positieve beslissing tot verdere ontwikkeling na markt goedkeuring van de eerste OMP voor een specifieke weesziekte. Hier blijkt uit dat het instrument van markt exclusiviteit *geen* barrière is voor andere bedrijven om te investeren in weesziekten met een goedgekeurde OMP. Meer algemeen blijkt uit onze resultaten dat een instrument, met als doel farma innovaties voor onvervulde medische behoefte te stimuleren, *niet* bijdraagt aan de lock-in van maar één technologie (dwz. één goedgekeurde OMP). Verder verwachten bijna alle FOMP sponsors 'significant benefit' (aanzienlijk voordeel) te rechtvaardigen door een verbeterde effectiviteit aan te tonen in vergelijking met de eerste goedgekeurde OMP.

Het doel van deze thesis was de (scheve) verdeling van OMP's verder toe te lichten. Er is geconcludeerd dat er een scheve verdeling is voor zowel de translatie van weesziekte onderzoek in de start van een weesgeneesmiddel programma, als voor goedgekeurde OMP's, als ook voor FOMP ontwikkeling. De huidige wetgeving is dus niet voldoende om alle patiënten die lijden aan een zeldzame ziekte toegang te geven tot behandelingen met dezelfde kwaliteit als andere patiënten. Als gevolg hiervan en om de scheve verdeling aan te pakken, moeten er additionele (financiële) stimuleringsmaatregelen worden geïmplementeerd om geneesmiddelenontwikkeling voor weesziekten met een prevalentie lager dan 1/100.000 te stimuleren. Daarnaast hebben de grote sponsors betrokken in FOMP ontwikkeling vaak de benodigde ervaring om een FOMP op de markt te brengen, echter ook de FOMP's die in het bezit zijn van MKB's moeten op de markt komen. Om de scheve verdeling aan te pakken is het dus ook belangrijk om op MKB's te focussen. De EMA richt zich hierop door middel van het geven van wetenschappelijk advies en

technische bijstand aan deze sponsors en door de oprichting van een MKB bureau, wat zich richt op aan regulatie gerelateerde behoeften van MKB's. Gebaseerd op de resultaten van deze thesis dienen nieuwe beleidsmaatregelen met betrekking tot het stimuleren van farma innovaties (voor onvervulde medische behoefte) rekening te houden met de volgende twee issues: het gelijk aanpakken van onvervulde medische behoefte en focussen op onervaren sponsors (meestal MKB's) om ook hen mogelijkheid te geven optimaal te kunnen profiteren van de aangeboden stimuleringsmaatregelen van een regulatie.

LIST OF ABBREVIATIONS, FIGURES AND TABLES

List of abbreviations

- **CHMP** **C**ommittee for **M**edicinal **P**roducts for **H**uman Use
- **CI** **C**onfidence **I**nterval
- **COMP** **C**ommittee for **O**rphan **M**edicinal **P**roducts
- **EC** **E**uropean **C**ommission
- **EMA** **E**uropean **M**edicines **A**gency
- **EODR** **E**uropean **O**rphan **D**rug **R**egulation
- **EPAR** **E**uropean **P**ublic **A**ssessment **R**eport
- **EURORDIS** **Eur**opean **O**rganization for **R**are **Dis**orders
- **FDA** **F**ood and **D**rug **A**dministration
- **FD&C Act** **F**ood, **D**rug & **C**osmetic **Act**
- **FOMP** **Follow-on O**rphan **M**edicinal **P**roduct
- **GSK** **G**laxo**S**mith**K**line
- **ICD-10** **I**nternational **C**lassification of **D**iseases version **10**
- **NIH** **N**ational **I**nstitute of **H**ealth
- **NORD** **N**ational **O**rganization of **R**are **D**iseases
- **OD** **O**rphan **D**esignation
- **ODA** **O**rphan **D**rug **A**ct
- **OMP** **O**rphan **M**edicinal **P**roduct
- **OOPD** **O**ffice of **O**rphan **P**roduct **D**evelopment
- **OR** **O**dds **R**atio
- **RGO** **R**aad voor **G**ezondheids**o**nderzoek
- **SME** **S**mall- and **M**edium-sized **E**nterprises (in Dutch: MKB (see samenvatting))
- **SofO** **S**ummary **of O**pinion
- **STOA** **S**cientific **T**echnology **O**ptions **A**ssessment Unit
- **WGM** Stuurgroep **W**ees**g**enees**m**iddelen
- **WHO** **W**orld **H**ealth **O**rganization

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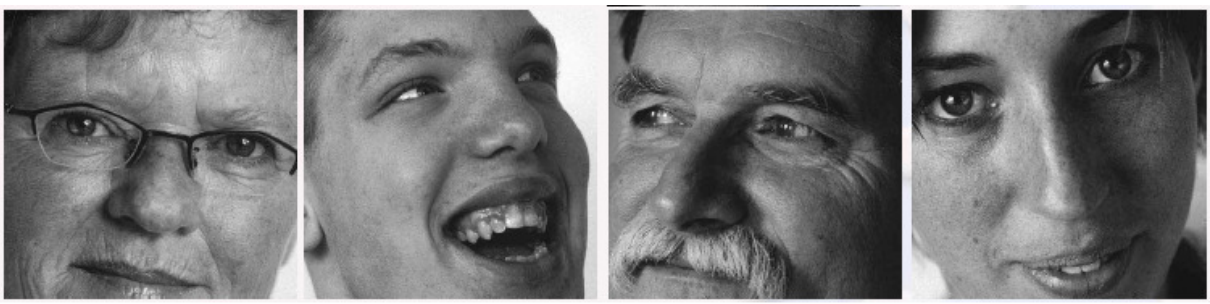
TERMINOLOGY

The term rare disease is most commonly used within the orphan drug field. However, synonyms of this concept are orphan disease and rare indication. Within this thesis these terms are interchangeable used. Furthermore, the orphan drug field is highly regulated and as a consequence, a lot of different terms and phrases are used within the regulations. More detailed, both the European Orphan Drug Regulation in Europe and the Orphan Drug Act in the USA have their own vocabulary and use different terms with the same meaning (e.g. authorization (Europe) vs. approval (USA)). Within this thesis aspects of both orphan legislations are discussed and as a result, terms of both legislations are presented.

(copied from Stuurgroep Weesgeneesmiddelen, 2010a)

INTRODUCTION



(copied from Stuurgroep Weesgeneesmiddelen, 2010a)

Chapter 1 – INTRODUCTION

1.1 Background

On the 25th of February 2010, the Dutch newspapers BN de Stem and Parool both published an article named "patient met zeldzame ziekte wordt vergeten". The articles described just a few of the difficulties experienced by patients suffering from a rare indication. More specific, a rare disease is a life threatening or seriously debilitating disease with such a low prevalence that combined efforts are necessary to prevent a high morbidity and, perinatal and early mortality (Stuurgroep Weesgeneesmiddelen, 2009). Although relatively few people are affected by each rare disease, in total more than 55 million patients in both Europe (EU) and the United States of America (USA) suffer from one of the known rare diseases (Heemstra, 2010). At this moment, between 5,000 and 8,000 different rare diseases are identified and every year about 250 new ones are discovered (Wästfelt et al., 2006). In the future, only more orphan diseases will be identified as a result of our improving knowledge on disease biology and genomics (Heemstra et al., 2008a; Haffner et al., 2002). This knowledge may result in the subdivision of more prevalent indications into several distinct rare indications (e.g. leukemia in acute promyelocytic leukemia, acute myelomonocytic leukemia etc.) (Heemstra et al., 2008a; Haffner et al., 2002). As yet, for many rare indications no adequate treatments are available (Stolk et al., 2005).

This lack of adequate treatments could, among others, be explained by the fact that drugs for rare indications, so-called orphan drugs, can be considered as incomplete pharmaceutical innovations (Boon et al., 2010). To become successful, a pharmaceutical innovation has to comply at least the three following prerequisites: medical need (i.e. an existence of an unmet medical need), technological feasibility (i.e. options for an effective and safe medicine) and economic profitability (i.e. value creation for the industry and investors is present) (based on Van Noordwijk (1984) in Buurma et al., 2005). In the case of an orphan drug the first two requirements are met, however, the economic profitability could be questioned. This lack of economic profitability is related to the high costs and risks of drug development, together with difficulties in conducting clinical trials for these orphan diseases on the one hand, and a small market size on the other hand (Heemstra et al., 2008a). As a result, despite the high unmet medical need, most pharmaceutical companies are not interested in developing a treatment for an 'orphan' (Boon and Moors, 2008; Heemstra et al., 2008a; Dear et al., 2006). Finding effective and safe treatments for the patients suffering from rare indications is therefore an important public health issue (Heemstra, 2010; Stolk et al., 2005; Eurordis, 2005).

As a consequence, and to stimulate pharmaceutical innovation, several policy measures have been introduced by the authorities. The relation between these policy measures and innovation is an interesting question with regard to drug development and unmet medical needs. The Food and Drug Administration (FDA) in the USA introduced in 1983 the first legislative framework for rare diseases: the Orphan Drug Act (ODA) (FDA, 1983), followed by Singapore in 1991, Japan in 1993 and Australia in 1998. Finally, in April 2000, the European Medicines Agency (EMA) in Europe introduced their legislation, the European Orphan Drug Regulation (EODR) (Dear et al., 2006; Wästfelt et al., 2006). The rest of this thesis focuses on both Europe and the USA. On the one hand, because the markets in Europe and the USA are most attractive for pharmaceutical companies due to their size. On the other hand, because data of Europe and the USA can relatively easy be obtained from sources in the public domain.

The ODA and the EODR are aimed at stimulating the research and development of medicinal products for orphan diseases by providing (financial) incentives to the pharmaceutical industry (EMA, 2009; FDA, 1983). Thereby, they aim to give patients affected by rare indications access to treatments having the same quality as other patients (EMA, 2009; Dear et al., 2006). The ODA of the USA and the EODR of Europe have much in common, although some differences regarding their incentives as well as criteria exist. A short overview of both the ODA (USA) and the EODR (Europe) is therefore provided hereafter, while a more extensive overview of the legislations regarding their history, facts and figures is presented in appendix I of this thesis.

According to the ODA, orphan diseases have a maximum of 200,000 patients in the USA, which is comparable to 7.5 patients per 10,000 inhabitants (Rinaldi, 2005; Haffner et al., 2002). The EODR of Europe uses a maximum prevalence of 5 patients per 10,000 inhabitants and moreover, the EODR has two additional requirements. Firstly, a rare disease has to be life threatening or seriously debilitating (Heemstra et al., 2008b) and secondly, sponsors[(1)] have to justify that their medicinal product is of significant benefit compared to existing treatments at the time of designation (COMP, 2009; Voordouw, 2009). Significant benefit is defined within Europe as "a clinically relevant advantage or a major contribution to patient care" (COMP, 2009: 4). Moreover, assumptions have to be plausible and, if possible, based on pharmacological principles (COMP, 2009). In general, significant benefit is justified by "demonstration of potentially greater efficacy, an improved safety profile and/or more favorable pharmacokinetic properties than existing methods" (COMP, 2009: 4).

If a medicinal product complies to these criteria, sponsors are able to obtain an orphan designation (OD) for their medicinal product at any stage during development from the authorities (COMP, 2009; Heemstra et al., 2008a and 2008b; Dear et al., 2006; Rohde, 2000). These orphan medicinal products (OMP's)[(2)] are then entitled to several incentives, like fee reduction, protocol assistance and free scientific advice. In addition, the ODA also provides tax incentives to the sponsors of the OMP's (Heemstra et al., 2008b). Nevertheless, the most important innovation encouraging incentive for these unmet medical needs is a market exclusivity period of seven years (USA) or ten years (Europe) upon authorization (Heemstra et al., 2008b; Dear et al., 2006). During this period of exclusivity, no similar competitive product can obtain approval from the authorities unless (clinical) superiority is demonstrated (Dear et al., 2006; Meyers and Lipucci Di Paola, 2003).

1.2 Problem description

The introduction of both legislations resulted in 349 authorized OMP's in the USA by the FDA and around 2,185 medicinal products that obtained an OD of the FDA up to and including June 2010 (based on data from the FDA, 2010a). In Europe, on the other hand, 58 OMP's are approved by the EMA and more than 725 medicinal products received an OD from the EMA up to and including June 2010 (based on data from European Commission, 2010a; Orpha.net, 2010a).

As a result, different stakeholders (e.g. patients, industry and policy makers) have recognized the huge impact of both orphan legislations on orphan drug development (Stolk et al., 2005; Rinaldi, 2005; Haffner et al., 2002). It is

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(1) sponsor means "any legal or natural person, established in the Community [i.e. Europe], seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product" (Commission of the European Communities, 2000: 2).

(2) an Orphan Medicinal Product (OMP) means "a medicinal product designated as such under the terms and conditions of this [i.e. orphan drug] regulation" (Commission of the European Communities, 2000: 2). Thus, a medicinal product has to obtain an Orphan Designation (OD) from the authorities to become an Orphan Medicinal Product (OMP).

furthermore also widely acknowledged that the incentives have been successful in stimulating the discovery and development of OMP's (Heemstra et al., 2009). Nevertheless, from all the incentives is the instrument of market exclusivity by far the most important instrument encouraging the industry to develop an OMP (Dear et al., 2006; Commission of the European Communities, 2006; Meyers and Lipucci Di Paola, 2003).

Despite the progress made during the last decades regarding the above mentioned number of (authorized) OMP's, for many rare indications, however, no safe and effective treatments are available yet (Stolk et al., 2005). This is partly explained by the high and increasing number of rare diseases (Wästfelt et al., 2006). However, at the same time, some rare disease(s) (classes) are associated with a high number of (approved) OMP's. Especially oncologic and metabolic disorders are responsible for a high percentage of (approved) OMP's, as depicted in figure 1.1 for Europe (EMA, 2010b; EMA, 2008; Meyers and Lipucci Di Paola, 2003; Haffner et al., 2002). More specific, four different groups of rare indications could be discerned regarding the development of OMP's, as depicted in box I of this thesis.

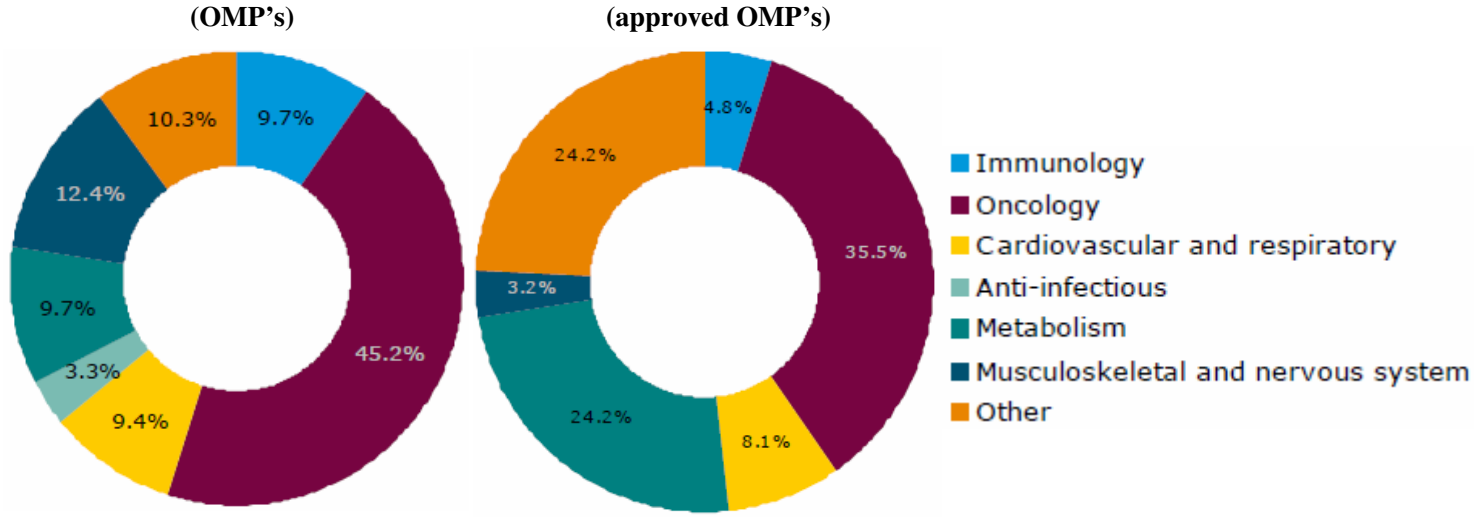


Figure 1.1: Distribution OMP's and approved OMP's per therapeutic area in Europe (both figures copied from EMA, 2010b: 2 and 5)

BOX I – 4 GROUPS OF RARE INDICATIONS

- **Group 1 – rare indications having one OD, but no approved OMP**

e.g. Wiskott-Aldrich syndrome

- **Group 2 – rare indications having more than one OD, but no approved OMP**

e.g. Duchenne muscular dystrophy and cystic fybrosis

- **Group 3 – rare indications having no OD, but one approved OMP**

e.g. NAGS-deficiency, mucopolysaccharidosis type I and tyrosinaemia type I

- **Group 4 – rare indications having more OD's and at least one approved OMP**

e.g. Pulmonary arterial hypertension, renal cell carcinoma and chronic myeloid leukemia

As presented in box I, for some rare indications (group 1 and 2) no treatments have come on the market, while for other rare indications (group 3 and 4) an authorized OMP is available yet. This availability of an authorized OMP proves that a successful innovation (approved OMP) is possible for these rare diseases. Furthermore, for several of these indications (group 4), other follow-on OMP's (FOMP's) are in development or sometimes even authorized.

As a result, there is thus a (skewed) distribution for orphan drug development and more detailed, for follow-on OMP (FOMP) development. Consequently, part of the patients suffering from a rare indication never get access to better, and finally optimal, treatments for their orphan disease, despite the fact that the orphan legislations aim to give patients of rare indications access to treatments having the same quality as other patients. Finding factors that explain this (skewed) distribution will therefore be helpful to give implications regarding possible refinements of the existing legislations and as a result, to give patients access to better treatments.

Chapter 2 – AIM, RESEARCH QUESTIONS AND RELEVANCE

2.1 Aim

Resulting from the problem description, this thesis aims to further elucidate the (skewed) distribution of orphan medicinal products, especially in relation to the presence of FOMP's for rare diseases with an approved OMP. As a result, this research contributes to a better understanding of orphan drug development and more detailed, to the development of FOMP's.

Earlier research of Heemstra et al. (2009) determined the relation between disease-specific characteristics and the chance for a rare disease to obtain at least one OMP. Heemstra et al. (2009) concluded that the disease class, the disease prevalence and the disease-specific scientific output do matter in the translation of rare disease research into subsequent orphan drug development. However, the presence of an OMP is only an indicator for successful translation of rare disease research into the start of an orphan drug development program, whether this translation resulted in an *authorized* OMP was not determined by Heemstra et al. (2009).

Heemstra et al. (2009) only focused on one aspect of orphan drug development, i.e. disease-related characteristics. To get a complete understanding of orphan drug development, besides disease-related, also product- and market-related characteristics have to be taken into account, since successful drug development requires at least the three prerequisites medical need (disease-related), technological feasibility (product-related) and economic profitability (market related) (Moors, 2010 (based on Van Noordwijk (1984)). Milne (2002) furthermore argued that market and technological factors, like the faster clinical development time, could help make orphan drug development even more attractive. As a result, this thesis aims to identify factors explaining the (skewed) distribution regarding the development of FOMP's for rare diseases with an approved OMP by means of disease-, product- and market-related characteristics.

Successful orphan drug development is related to sponsor characteristics (e.g. Regnstrom et al., 2010; Heemstra et al., 2008a; Rzakhanov, 2008). Therefore, this thesis also aims to investigate the characterization of the sponsors of the FOMP's in development for rare diseases with an approved OMP to get the most complete insight in FOMP development. Furthermore, the development of FOMP's puts the instrument of market exclusivity in another perspective, because sponsors of FOMP's have to be satisfied with a shared exclusivity (e.g. half or third) together with sponsors of earlier authorized OMP's for the same rare indication. Nachbar and Tinselboer (2008) therefore proposed that market approval of the first OMP for a specific rare indication is a disincentive for other sponsors to continue further development. As a consequence, the instrument of market exclusivity is able to hamper further development of better and more specific treatments for patients suffering from a rare disease. Whether the market exclusivity instrument hampers the availability of better and finally optimal treatments will be investigated in this thesis by describing to what extent, and for what reason, sponsors decide to continue FOMP development after the market authorization of the first OMP for the same rare indication.

In conclusion, the aim of this thesis is to further elucidate the (skewed) distribution regarding the development of FOMP's for rare indications with an authorized OMP, which will be done by examining two 'blocks'. Firstly, this thesis aims to identify factors explaining the (skewed) distribution. And thereafter, this thesis also aims to describe the characteristics of the sponsors of the FOMP's in development.

2.2 Research questions

Following the objectives, the main research question to be answered in this thesis is:

Which factors explain the development of FOMP's and how can the sponsors of FOMP's be characterized?

In order to answer this main research question, the following six sub-questions are set up:

(1) To what extent have rare indications with an authorized OMP at least one FOMP?
(2) Which factors explain that some rare indications with an authorized OMP have at least one FOMP and other rare indications with an authorized OMP have no FOMP?
(3) How many FOMP's are identified for the rare indications with an approved OMP and at least one FOMP?
(4) What are the sponsor characteristics of the FOMP's in development?
(5) To what extent do sponsors of FOMP's decide to terminate or continue further development after the market authorization of the first OMP for the same rare indication, and why?
(6) Which policy implications regarding stimulating pharma innovation (for unmet medical needs) by means of regulation could be derived from the results of this thesis in general?

Research approach

The best way to get insight in the main research question of this thesis is by investigating rare indications with an authorized OMP, thereby discerning two groups:
(1) rare indications having an authorized OMP, and **no FOMP**;
(2) rare indications having an authorized OMP, and **at least one FOMP**.

By a comparison of the two groups possible factors explaining the development of FOMP's can be identified (i.e. block one). More detailed, the framework of Van Noordwijk (1984) is used to identify these possible factors. Van Noordwijk (1984) identified three prerequisites that comply to successful pharmaceutical innovations, i.e. medical need, technological feasibility and economic profitability. The second sub-sample is thereafter further elaborated in this thesis to be able to characterize the sponsors of FOMP's in development of rare diseases with an approved OMP (i.e. block two).

Furthermore, this thesis focuses on Europe due to the mentioned differences in criteria and incentives between the different orphan drug legislations. Moreover, the study period of this thesis is demarcated from 1 January 2001 up to 31 December 2008. This time period is most suitable, on the one hand, because before the year 2001 no OMP's obtained market approval in Europe due to the absence of the European Orphan Drug Regulation (EODR). On the other hand, delineating to the end of 2008 makes it possible to examine at least one complete (i.e. financial) year (i.e. 2009) of the sponsors of the FOMP's and to obtain thus the most full results regarding their characterization.

Finally, central to this thesis is the concept of the development of at least one FOMP. To avoid inconsistencies in the rest of this thesis, this concept is defined here as follows:
Rare indications with an authorized OMP have at least one FOMP, if there is:
(1) another authorized OMP for the same rare indication in Europe;
(e.g. both Fabrazyme and Replagal are approved for the treatment of Fabry disease in Europe)
(2) another OMP for the same rare indication in Europe.
(i.e. another medicinal product with an European OD)

2.3 Relevance

➢ 2.3.1 Scientific relevance

The 'innovation deficit' of the pharmaceutical industry is probably one of the most discussed subjects of the last decade within the health care industry (Boon et al., 2010). Despite the enormous increasing amounts of R&D, the launch of new (and innovative) medicines on the market has declined (Van Delden, 2008; Gassmann et al., 2004; Rang, 2006; Buurma et al., 2005). This deficit could partly be explained by too much emphasis of pharmaceutical companies on follow-on and generic drugs (Boon et al., 2010). Moreover, the last decades the strategy of big pharmaceutical companies has been aimed at developing blockbusters, drugs with at least 1 billion US dollar in annual sales, covering the overall costs of maintaining their product pipeline (Gassmann et al., 2004; Rang, 2006). As a result, the industry has been less focused on developing medicines for unmet medical needs, e.g. orphan and neglected diseases (Boon et al., 2010). However, with the declining sales and expiring patents of blockbusters, big pharmaceutical companies begin to realize that their strategy is not sustainable anymore to meet the growth expectations of the future (Datamonitor, 2009; DrugResearcher, 2006; Gassmann et al., 2004). Consequently, the pharmaceutical industry has to move towards a more sustainable niche-buster model having smaller markets characterized by high unmet medical needs (DrugResearcher, 2006). From an industry perspective niche-markets have substantial sales potentials, as a result of lower marketing costs, limited competition, support from regulatory authorities and less generic competition (DrugResearcher, 2006). Besides these potentials, however, these markets are more uncertain and less concrete, which hampers the pharmaceutical industries' willingness to invest (Boon et al., 2010).

To stimulate the willingness of the pharmaceutical industry to invest in these markets with unmet medical needs, and thereby addressing the innovation deficit, both the FDA in the USA and the EMA in Europe implemented policy measures aimed at encouraging pharmaceutical innovations. The FDA introduced in 2004 their Critical Path Initiative, which aimed to improve predictability and efficacy of drug development (FDA, 2004). The EMA followed in 2005 with their Roadmap to 2010 (as of January 2010 replaced by the Roadmap to 2015), aimed at improving the regulatory environment and stimulating innovation as well as research and development (EMA, 2005). Besides the in April 2000 introduced European Orphan Drug Regulation, the EMA also implemented in January 2007 their Pediatric Regulation and in December 2007 the Innovative Medicines Initiative to address the innovation deficit of the industry (Heemstra et al., 2008b; Council of the European Union, 2007; EMA, 2010c).

Among these policy measures, the European Orphan Drug Regulation (EODR) is a valuable measure encouraging the transition from science towards real innovation that benefit the European economy as well as patients affected by rare indications (Heemstra et al., 2008b). The EMA also reviewed the 'innovativeness' of medicinal products applying for an OD and concluded that approximately half (53 %) of all the OD applications constitute of novel and/or innovative medicinal products (Commission of the European Communities, 2006). Nowadays, up to June 2010, around 730 medicinal products received an OD and 58 OMP's have been authorized in Europe (based on data from Orpha.net, 2010a; European Commission, 2010a). These numbers demonstrate that the incentives, and especially the instrument of market exclusivity, have been successful in encouraging pharma innovation for unmet medical needs, particularly in small and medium sized enterprises (Heemstra et al., 2009). Besides this, Wellman-Labadie and Zhou (2010) concluded that at least 9 % of the approved OMP's have reached blockbuster status (e.g. Cerezyme® and Glivec®), which proves that even an orphan drug is interesting from a business perspective.

The success of the EODR, in combination with the mentioned decreasing probability of success of the blockbuster strategy, explains the growing interest of big pharma for the orphan drug field. For example, the pharmaceutical company Pfizer announced in December 2009 that it's planning to launch a new drug for Gaucher disease after acquiring Protalix's drug taliglucerase alfa (Hensley, 2009; Pollack, 2009). Furthermore, Pfizer has established a 'rare disease research unit' to focus on orphan drug development (PBR, 2010). Finally, GlaxoSmithKline (GSK) has recently licensed a compound for the disease duchenne muscular dystrophy from the Dutch company Prosensa (GSK, 2009; EuroPharmaToday, 2009).

In conclusion, the pharmaceutical industry has to move towards a more sustainable niche-buster model having smaller markets characterized by high unmet medical needs (e.g. orphan diseases) due to the decreasing likelihood of success of the blockbuster strategy. To stimulate the willingness of pharmaceutical companies to invest in these markets different policy measures are implemented. The EODR is, among others, a valuable measure encouraging pharma innovations for these unmet medical needs. Approved OMP's as Glivec® and Cerezyme® prove that even focusing on niche-buster markets can result in the development of blockbusters. As a result, there appears to be a growing interest of (big) pharma to invest in the orphan drug field.

➢ 2.3.2 Social relevance

Although relatively few people are affected by each of the 5,000 to 8,000 known orphan diseases, in total more than 55 million patients in Europe and the USA together suffer from such a disease. All these patients and their families are experienced with a wide range of difficulties (e.g. lack of correct diagnosis, lack of information, lack of adequate healthcare) related to the rarity of their disease. Finding methods to treat those patients is therefore an important public health issue (Heemstra, 2010; Eurordis, 2005). As a consequence, the orphan legislations were implemented with the aim of giving patients affected by a rare disease access to treatments with the same quality as other patients.

Despite the mentioned successes with regard to the availability of authorized OMP's since the introduction of the legislations, for many orphan diseases no adequate treatments are available yet. Earlier research already concluded that this could be explained by the high number of different rare indications (Wästfelt et al., 2006). Furthermore, Heemstra et al. (2009) concluded that disease-specific characteristics do matter in the translation of rare disease research into orphan drug development. However, at the same time, some rare diseases are associated with a high number of OMP's, whereas others have none. For several of the rare indications with an authorized OMP, follow-on OMP's (FOMP's) are in development or even authorized.

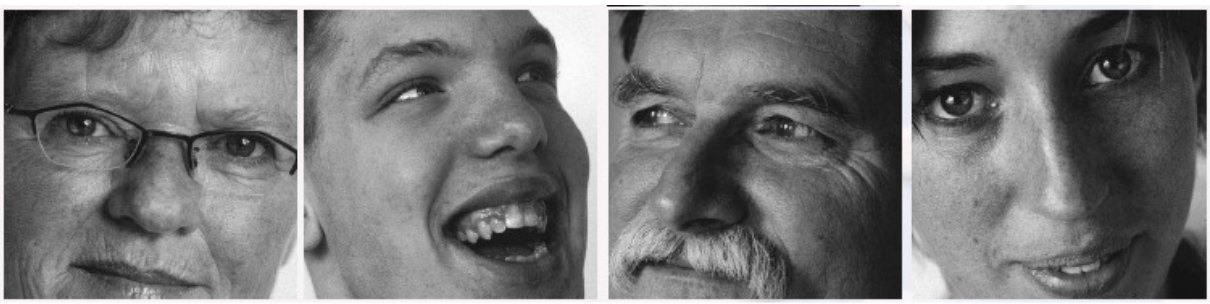
To summarize, there appears to be a (skewed) distribution regarding orphan drug development, and more specific with regard to follow-on OMP (FOMP) development. As a result, part of the patients affected by a rare indication never get access to better, and finally optimal, treatments for their indication, despite the fact that the legislations are aimed at giving patients with rare indications access to treatments with the same quality as other patients. As a consequence, finding factors explaining this (skewed) distribution will thus be helpful to give recommendations with regard to possible refinements of the existing legislations and as a result, giving patients access to better, and finally optimal, treatments.

2.4 Outline thesis

The previous chapters set the scene of this thesis by elaborating the problem description, aim, research questions and relevance of this thesis. These first two chapters together form an introduction on the rest of this thesis. In the next chapter the theoretical background used in this thesis is elaborated. This theoretical background tries to give a preliminary answer on the main research question stated in the introduction. Chapter 4 is thereafter dedicated to the operationalization of the variables which are introduced in the theoretical background. The methodology used in this thesis is elaborated in chapter 5. In the methodology, the research design, sample selection, data collection and data analysis are discussed respectively. The next chapter, chapter 6, gives an overview of the main results of the performed studies regarding both block one and two of this thesis. Chapter 7, to conclude, discusses the main findings and conclusions, among others, by comparing the findings with earlier research. In addition, the general conclusion is presented by giving an answer on the main research question of this thesis. Subsequently, the policy implications are elaborated. The last paragraph of chapter 7 discusses all performed steps of the empirical cycle of this thesis.

(copied from Stuurgroep Weesgeneesmiddelen, 2010a)

THEORETICAL BACKGROUND



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Chapter 3 – THEORETICAL BACKGROUND

This chapter provides the theoretical background and conceptual model of this thesis to give a preliminary answer on the stated research question. However, the research question consists of two blocks: on the one hand explaining the development of FOMP's, on the other hand, characterizing the sponsors of FOMP's. As a result, theoretical backgrounds regarding each block are provided within this chapter. The presented conceptual model includes both block one and two in order to show their relation, as depicted in figure 3.2.

3.1 The development of FOMP's (block one)

The theoretical framework used to identify possible factors explaining the development of FOMP's for orphan diseases with an authorized OMP is based on requirements that comply to a successful pharmaceutical innovation. The dependent variable is therefore the development of at least one FOMP. This variable is already defined in this thesis, however, to summarize, a rare indication has at least one FOMP if there is another OMP or approved OMP for the same rare indication in Europe (for further explanation see paragraph 2.2).

Van Noordwijk (1984) identified the following prerequisites complying to successful pharmaceutical innovations: technological feasibility, economic profitability and medical need. A pharmaceutical compound ideally complies to all these three prerequisites, as depicted within figure 3.1 (Van Noordwijk (1984) in Buurma et al., 2005). More detailed, the diagram of Van Noordwijk (1984) illustrates a diverse range of forces involved in drug development, namely pharmaceutical-technical, medical-therapeutic and socio-economic factors (Buurma et al., 2005).

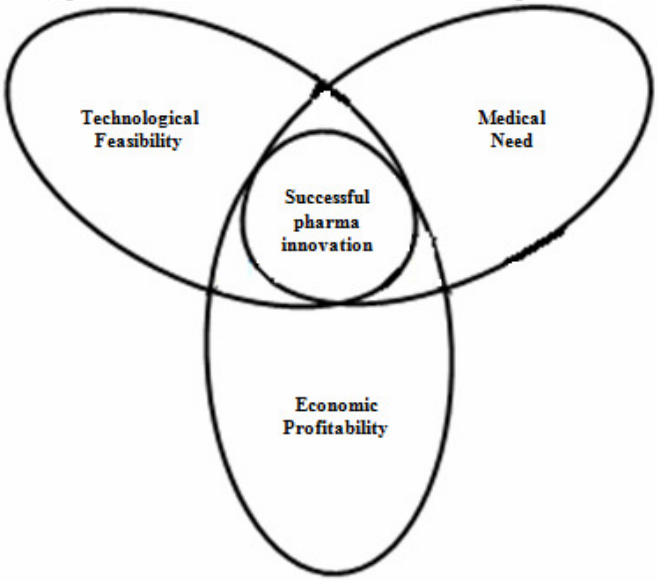

Figure 3.1: Prerequisites successful pharmaceutical innovation (adapted from Van Noordwijk (1984) in Buurma et al., 2005)

Khilji et al. (2006) furthermore developed an innovation model for biotech companies including three factors, i.e. organizational capabilities, market forces and technology and science. The latest two factors of the model of Khilji et al. (2006) appear to be associated with the requirements economic profitability and technological feasibility of Van Noordwijk (1984) respectively. Furthermore, regarding orphan drug development, Milne (2002) argued that market (related to economic profitability) and technological (related to technological feasibility) forces could help make the orphan drug field even more attractive for the pharmaceutical companies. Finally, Heemstra et al. (2009) argued that disease-related factors do matter in the translation of rare disease research into subsequent orphan drug development. These disease-related factors seem to be related to the prerequisite medical need of Van Noordwijk.

To summarize, the three prerequisites of Van Noordwijk (1984) enclose a wide range of factors that appear to be related to successful pharmaceutical innovations and therefore, they provide a rather complete overview regarding possible factors explaining the (skewed) distribution of FOMP's for rare indications with an approved OMP. This thesis, however, adapted the three prerequisites of Van Noordwijk (1984) to get more broad characteristics that better fit to the earlier mentioned research and therefore to the orphan drug field. As a result, the following three characteristics were identified in this thesis: **market-related** characteristics (adapted from economic profitability), **disease-related** characteristics (adapted from medical need) and finally, **product-related** characteristics (adapted from technological feasibility). These three characteristics related to successful pharma innovations are elaborated hereafter based on research with regard to orphan drug development (e.g. Regnstrom et al., 2010; Heemstra et al., 2008a and 2009; Rzakhanov 2008; Milne, 2002).

➢ 3.1.1 Market-related characteristics

Acemoglu and Linn (2003) concluded that the potential market size of users is a determinant for innovation in the pharmaceutical industry. The concept of market-related characteristics is therefore further elaborated by means of the disease prevalence, the turnover of the first approved OMP and whether the first approved OMP is designated and/or approved outside Europe, because these dimensions give an indication of the potential market size.

Disease prevalence

The likelihood to start an orphan drug development program is associated with the prevalence of the rare disease. "A disease with a prevalence between 10 and 50 per 100,000 had a more than threefold higher chance of obtaining at least one product with a designation than a disease with a prevalence of 0.1-0.9 per 100,000" (Heemstra et al., 2009: 1169). As mentioned earlier, Acemoglu and Linn (2003) examined the relationship between market size and innovation in the pharmaceutical industry. A 1 % increase in the potential size of the market leads to an increase of 4-7.5 % in the number of new drugs in a specific drug category (Acemoglu and Linn, 2003). Although orphan drugs were not included in their study, the authors investigated whether their results were robust for orphan drugs. Acemoglu and Linn (2003) concluded that their results were nearly identical and that their model was thus robust for orphan drugs. As a result, the market size appears to be a predictor for the number of obtained drugs for that specific (rare) indication. Here, we use the prevalence of a specific rare indication as a surrogate marker for the potential market size of users.

Turnover first approved OMP

Orphan drugs are not expected to create high revenues for sponsors. More detailed, Alcimed (2004) estimated the annual sales of an approved OMP in Europe between the 100 million and 1.5 billion euro. In addition, Ariyanchira (2008) emphasizes that an increasing number of authorized OMP's reach annual sales exceeding 200 million US dollar. Moreover, Wellman-Labadie and Zhou (2010) argued that more than 9 % of the authorized OMP's in the USA reach annual sales exceeding the blockbuster threshold of 1 billion US dollar. Therefore, we use here the turnover of the first authorized OMP for a particular rare indication as a second surrogate market for market size.

First authorized OMP designated and/or approved outside Europe

An authorized OMP having an orphan designation or market approval outside Europe implies a (potential) bigger market for the sponsor of that approved OMP, because more patients have access to the treatment. Sponsors are therefore able to generate more sales. This variable is therefore used here as a last surrogate marker regarding the size of the market.

➢ 3.1.2 Product-related characteristics

The concept of product-related characteristics is elaborated using the scientific output for a specific rare indication and the pharmaceutical formulation of the first authorized OMP. Research output is related to the understanding of diseases, which is in general necessary to start successful drug discovery and development programs (Heemstra et al., 2009). The pharmaceutical formulation, on the other hand, is included because this aspect is for patients an important factor regarding their treatment (e.g. Reig et al., 2006).

Disease-specific scientific output

A high number of scientific publications for a rare indication increase the likelihood of obtaining an OD for that specific disease. Rare diseases with more than 600 scientific articles have a more than 2-fold higher probability to obtain at least one medicinal product with an OD (Heemstra et al., 2009). Moreover, more research output results in more potential alternative targets for new treatments due to more (rare) disease knowledge.

Pharmaceutical formulation first authorized OMP

The formulation of a pharmaceutical compound does matter in, among others, patient compliance (e.g. Reig et al., 2006). Patients suffering from a rare indication, however, first need an adequate treatment. Thereafter, regarding improved treatments, also these patients prefer a more convenient administration mode for their treatment (e.g. an oral instead of parenteral formulation). As a result, sponsors of FOMP's may therefore contribute to patient care if their FOMP has a more convenient mode of administration in comparison with the first approved OMP.

➢ 3.1.3 Disease-related characteristics

Regarding the concept of disease-related characteristics, the disease class, duration of the disease, age of onset and the inheritance of the disease are included in this thesis. These four characteristics are disease aspects that are of influence on (orphan) drug development, as explained hereafter.

Disease class

Rare forms of cancer have the highest probability to obtain at least one medicinal product with an OD (Heemstra et al., 2009). This result confirms the literature findings that some disease classes, especially oncology, are related to more OMP's (Coté, 2010; EMA, 2008; Meyers and Lipucci Di Paola, 2003; Haffner et al., 2002). However, the findings imply that rare forms of cancer possess certain characteristics that explain successful translation of rare disease research into subsequent orphan drug development. Successful translation especially requires a sufficient understanding of the pathogenesis of the (orphan) disease, which is necessary for the discovery of drug leads and drug targets.

Chronic, childhood and inheritable disease

The duration, age of onset and inheritance of a disease may influence the development of FOMP's. For example, patients suffering from a chronic disease need a (life-)long treatment, which gives pharmaceutical companies the opportunity to earn back their investments over a longer period of time. Furthermore, conducting clinical trials for childhood diseases is expected to be more difficult due to ethical and practical implications. Consequently, orphan drug development for such diseases may be less attractive for pharmaceutical companies.

To summarize, the above mentioned theoretical background results in block one of the conceptual model, which is depicted in figure 3.2:

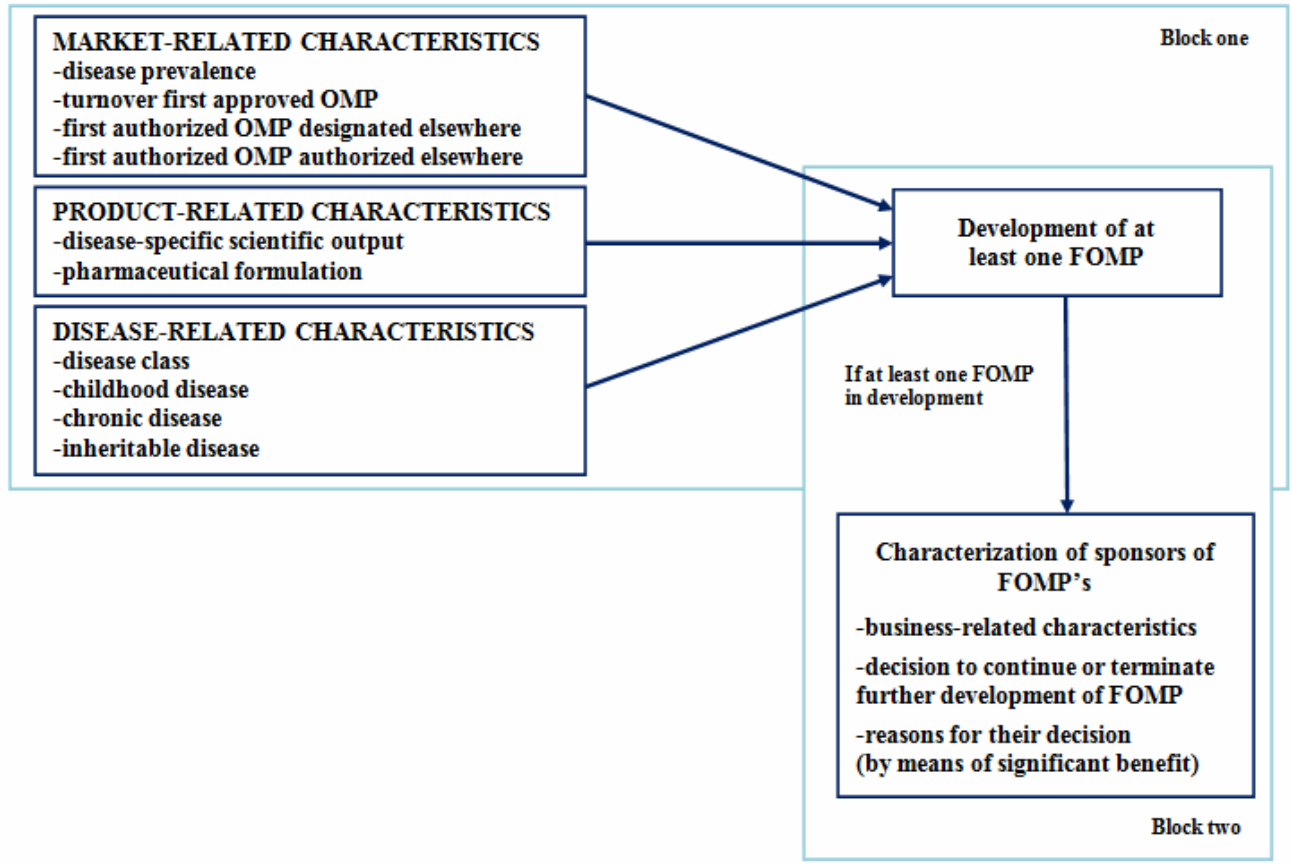

Figure 3.2: Conceptual model

3.2 Characterization of the sponsors of FOMP's (block two)

Paragraph 3.1 elaborated the possible factors that explain the development of FOMP's for rare indications with an authorized OMP (i.e. block one). As mentioned earlier, successful orphan drug development is related to sponsor characteristics. Block two of this thesis therefore aims to describe the characterization of the sponsors of FOMP's of rare indications with an approved OMP and at least one FOMP.

This characterization of the sponsors of FOMP's includes an analysis of the business-related characteristics of the sponsors due to results of Regnstrom et al. (2010), Heemstra et al. (2008a) and Rzakhanov (2008). Furthermore, the characterization describes to what extent, and for what reason, the sponsors of FOMP's decide to continue or terminate further development after the approval of the first OMP for the same rare indication (based on Nachbar and Tinselboer (2008)). We use here the concept of significant benefit (clinical superiority) to investigate for what reason sponsors of FOMP's decided to continue further development.

In conclusion, the characterization of the sponsors of FOMP's, as reflected in block two of the conceptual model, consists of the business-related characteristics (paragraph 3.2.1), the decision of sponsors to continue or terminate further development of their FOMP (paragraph 3.2.2) and the reason for this decision, analyzed by means of the concept of significant benefit (paragraph 3.2.3).

➢ 3.2.1 Business-related characteristics of the sponsors of FOMP's

The following business-related characteristics are included in this thesis and elaborated hereafter: experience of a sponsor, size of the company, type of the company and financials of the company.

Heemstra et al. (2008a) demonstrated that **experience** of a sponsor with regard to orphan drug development is an important predictor for subsequent approval of other OMP's. More detailed, sponsors who have already launched an OMP on the market have a 17-fold increased odds of getting market approval for subsequent OMP's (Heemstra et al., 2008a). In addition, Rzakhanov (2008) mentioned that having more than one orphan designation generates a higher market value for pharmaceutical companies compared to having exactly one OD. Although Heemstra et al. (2008a) did not find an association between the **size** of the company and successful market authorization, a strong statistically significant relation for the company's size and obtaining approval for a pharmaceutical compound was demonstrated by Regnstrom et al. (2010). The authors, however, focused here on the pharmaceutical industry in general instead of on the orphan drug field. Also the **financials** of the sponsor are expected to be related to orphan drug development. More specific, Rzakhanov (2008) confirmed that sponsors having more financial reserves are more willing to initiate an orphan drug development program. To conclude, the company's **type** does matter in the orphan drug field. Diversified firms are less involved in orphan drug development compared to non-diversified companies (Rzakhanov, 2008).

➢ 3.2.2 Decision of the sponsors of FOMP's to continue further development after approval of first OMP

The development of FOMP's shows, on the one hand, that pharmaceutical companies are not reluctant to initiate an orphan drug development program for these rare diseases. On the other hand, the development of FOMP's put the market exclusivity instrument in another perspective, because sponsors of FOMP's have to be satisfied with a shared (e.g. half or third) market exclusivity together with sponsors of earlier authorized OMP's for the same rare indication. Consequently, Nachbar and Tinselboer (2008) proposed that approval of the first OMP for a specific rare disease is a disincentive for other pharmaceutical companies to continue further development of their orphan drug program for that specific rare disease. As a result, the market exclusivity instrument is able to hamper further development of better and more specific treatments for patients suffering from a rare indication.

In general, this implies that an instrument, aimed at stimulating innovation for unmet medical needs, contributes to lock-in of one particular technology (the first authorized OMP). A lock-in means that one technology achieves complete market dominance at the expense of other technologies (FOMP's) (Arthur, 1989). Moreover, the author argued that, once such lock-in is achieved, this lock-in is able to prevent the development of potentially superior alternatives (from Foxon, 2007).

Whether the market exclusivity instrument hampers the availability of potential superior alternatives due to lock-in of the first authorized OMP, depends on to what extent sponsors of FOMP's are satisfied with a shared market exclusivity. The best way to analyze this, is elucidating the development process of FOMP's of the rare diseases with an authorized OMP. Examining this process makes it possible to determine whether sponsors terminate or continue further development of their orphan drug program after market approval of the first OMP for the same rare disease. As a result, the development of FOMP's is also characterized by the decision of sponsors of FOMP's regarding subsequent FOMP development after market approval of the first OMP for the same orphan disease.

➢ 3.2.3 Significant benefit as reason for decision FOMP sponsors

Besides determining to what extent sponsors decide to continue further development after market approval of the first OMP, this thesis also aimed to examine for what reason sponsors of FOMP's continued further development. To obtain market approval from the authorities and thus launch a FOMP on the market, sponsors of FOMP's have to show significant benefit, which is defined as "a clinically relevant advantage or a major contribution to patient

care" (COMP, 2009: 4). As a result, sponsors that are satisfied with a shared market exclusivity, and thus continue further development, are at least convinced that their FOMP is of significant benefit compared to earlier approved OMP's. This concept of significant benefit gives therefore this thesis insight in the reason of sponsors of FOMP's regarding their decision.

Already since the introduction of the orphan legislations, the concept of significant benefit (clinical superiority) has been subject of discussion because of its ambiguity (e.g. Reid, 2003; Bohrer and Prince, 1999). More detailed, Reid (2003) argued that the standards [of the FDA] to assess clinical superiority (significant benefit) are not that clear. Consequently, there has been misunderstanding since the introduction of the Orphan Drug Act in 1983 to what extent two competitive products are the same or sufficiently differ to be able to authorize the second OMP for the same rare indication (Dear et al., 2006; Bohrer and Prince, 1999). Reid (2003) especially referred to the discussion regarding the market approval of Fabrazyme and/or Replagal by the FDA in the USA. Both OMP's are nearly identical and both are authorized in Europe since August 2001, however, despite differences in their safety profiles, the FDA decided to only authorize Fabrazyme in the USA in April 2003 (Reid, 2003).

As a result, the EMA implemented a guideline (COMP/15893/09) regarding the concept of significant benefit in order to outline the necessary level of evidence to support assumptions of significant benefit. Significant benefit is justified in Europe by demonstrating an improved efficacy, a better safety profile or a contribution to patient care, as explained hereafter, and depicted in figure 3.3 (COMP, 2009).

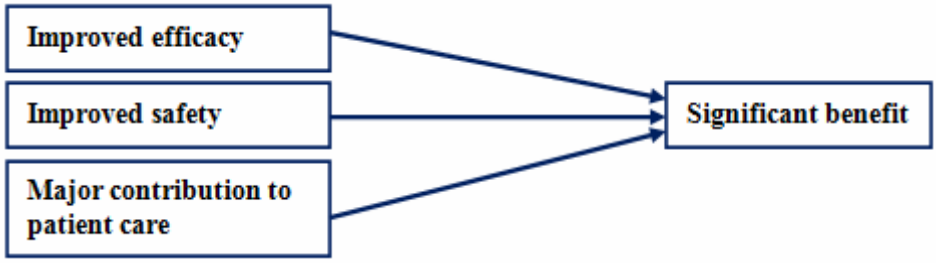

Figure 3.3: Assumptions of significant benefit of the EMA guideline (based on COMP, 2009)

Improved efficacy

A different mechanism of action can result in an improved efficacy, however, this fact is not enough to justify significant benefit (COMP, 2009). Sponsors have to support their assumptions with either pre-clinical or clinical data. If only pre-clinical data is available, comparisons based on experiments instead of on literature results are preferred by the EMA (COMP, 2009). If clinical data is available, a comparison of the findings of explanatory studies and data in literature is suitable to support assumptions of significant benefit (COMP, 2009). However, in all cases "significant benefit will be reassessed by the COMP before granting of the market authorization when complete clinical data are submitted" (COMP, 2009: 6 and 7).

Improved safety

The safety data of an OMP are mostly fully characterized after market launch of that specific OMP, because most adverse events are observed after administration of the drug to many patients under normal conditions. Sponsors arguing that significant benefit is expected to be related to safety have to support this expectation by either clinical data or references to pharmacological properties (COMP, 2009). Moreover, it is not possible to assume significant benefit based on a comparison of a theoretical risk of the approved OMP compared with a theoretical lack of risk

of the FOMP (COMP, 2009). A possible assumption of significant benefit with respect to the safety profile could be related to fewer side effects, for example, as a result of a different route of administration (COMP, 2009).

Major contribution to patient care

Assumptions of significant benefit based on a contribution to patient care are "mainly based on more convenient modes of administration improving patient compliance or an improved availability of the product for the patient population" (COMP, 2009: 7). However, clinical data is necessary to support assumptions of a more convenient mode of administration, because the advantages of another way of administration could be counteracted by side effects (e.g. oral administrated products could lead to gastrointestinal toxicity (COMP, 2009)). Finally, significant benefit can be assumed by improving the quality of life of patients and increasing the availability of the treatment in the whole community [i.e. Europe] (COMP, 2009).

In conclusion, this chapter provided the theoretical background that, on the one hand, explained the development of FOMP's by market-related, product-related and disease-related characteristics (block one). On the other hand, the theoretical background also provided the characterization of sponsors of FOMP's (block two). Block one, as well as block two, are summarized in the presented conceptual model in order to give a preliminary answer on the stated research question of this thesis. Regarding this question, it is expected that dimensions of market-related, product-related and disease-related characteristics explain the development of at least one FOMP for rare diseases with an authorized OMP. By analyzing the business-related characteristics and to what extent, and for what reason (significant benefit), sponsors of FOMP's decided to continue or terminate further development, this thesis is able to give an answer on block two of the research question.

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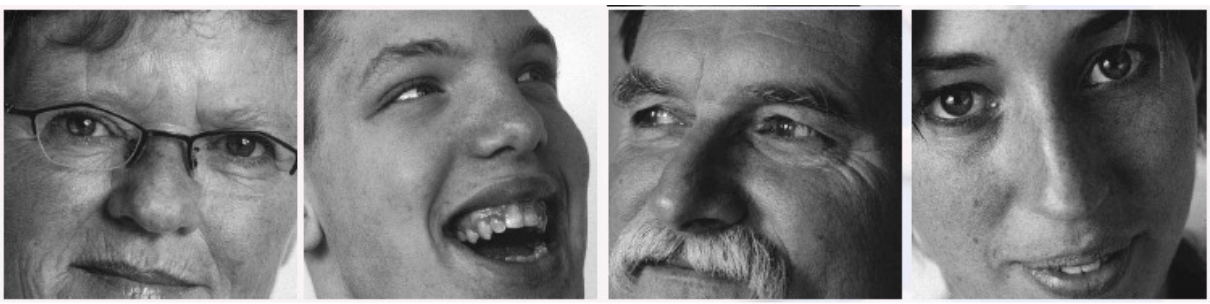
OPERATIONALIZATION



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Chapter 4 – OPERATIONALIZATION

In order to measure the variables of the conceptual model, dimensions and indicators for both the independent and dependent variables have to be elaborated. In this chapter variables of both block one and two of the conceptual model are operationalized. The operationalization of all concepts has been based, among others, on research from Heemstra et al. (2008a and 2009) and Rzakhanov (2008) and international used classifications.

4.1 Development of FOMP's (block one)

➢ 4.1.1 Follow-on OMP (FOMP) (dependent variable)

As mentioned earlier, rare indications with authorized OMP either have at least one FOMP or no FOMP in this thesis. A FOMP is defined as (see also paragraph 2.2.):

(1) another authorized OMP for the same rare indication in Europe;

(e.g. both Replagal and Fabrazyme are approved for the treatment of Fabry disease in Europe)

(2) another OMP for the same rare indication in Europe.

(i.e. another medicinal product with an European OD)

Only OMP's that were under development at or after the approval of the first OMP for the same rare disease are identified as FOMP in this thesis. As a result, an OMP designated before market approval of the first OMP for that specific disease, but whose development was terminated before authorization of the first OMP is **not** identified as FOMP in this thesis. To summarize, the variable is operationalized using a nominal scale by dividing rare diseases with an authorized OMP into the following two groups:

(1) rare indications having an authorized OMP, and **no FOMP** (**control group**);

(2) rare indications having an authorized OMP, and **at least one FOMP** (**experimental group**);

➢ 4.1.2 Market-related characteristics (independent variables)

Disease prevalence

The prevalence of a disease is defined as the proportion of the population affected by the disease at a specific time (from Buurma et al., 2005: 221). However, it is difficult to assess the exact prevalence of an orphan disease using the available sources in the public domain. This could be explained, among others, by a low level of consistency between studies and a poor documentation of the used methods (Orpha.net, 2009b). Orpha.net (2009b) therefore proposed that there is an overestimation of the prevalence for most rare diseases, because the few available studies are usually based on hospital data and done in regions of higher prevalence. As a result, Heemstra et al. (2009: 1169) concluded that "the estimates included in the Orpha.net report series are an indication of the assumed prevalence but might not be accurate". To overcome this limitation, Heemstra et al. (2009) decided to analyze the prevalence at disease class or prevalence group level instead of analyzing the disease prevalence at the individual disease level. Heemstra et al. (2009) did not include orphan diseases having a prevalence below 0.1 per 100,000, because drug development was found to be nearly absent in this group. However, some OMP's are authorized for rare indications having a prevalence below 0.1 per 100,000 (e.g. Orfadin for tyrosinaemia type 1 and Carbaglu for NAGS-deficiency). This thesis therefore discerned an additional category (< 0.1/100,000), besides the prevalence categories used by Heemstra et al. (2009). In conclusion, the prevalence is measured by an ordinal scale using the following categories: (1) < 0.1/100,000; (2) 0.1-0.9/100,000; (3) 1-9/100,000 and (4) 10-50/100,000.

Turnover first authorized OMP

It is difficult to predict the exact outcome range regarding the turnover of the first approved OMP in advance. The two categories of turnover are therefore in this thesis determined after data collection by dividing the cases of the control group into approximately two equal sub-groups based on the annual turnover of the first approved OMP's (based on Heemstra et al., 2009). As a result, this variable is measured by means of an ordinal scale. Furthermore, the maximum annual sales from 2001 to 2009 are assessed within this thesis, because sales of OMP's are growing slowly and therefore not much sales are expected during the first years after market launch (Milne, 2002).

First authorized OMP designated and/or approved outside Europe

Both variables are measured by analyzing whether the first authorized OMP also obtained another OD or another market authorization elsewhere in the world (i.e. outside Europe) (based on Heemstra et al., 2008a). As a result, this variable is measured in this thesis by a nominal scale (i.e. no other OD or another OD and no other approval or another approval).

➢ 4.1.3 Product-related characteristics (independent variables)

Disease-specific scientific output

This variable is defined as the number of scientific publications in PubMed for a specific rare disease (Heemstra et al., 2009). A search string is composed for each included rare indication to examine the number of publications in PubMed. These composed search strings are limited to the English language. Moreover, case and original reports are included while comments, letters and reviews are excluded from the analysis (based on Heemstra et al., 2009). Finally, Heemstra et al. (2009) delineated the search strings to the period 1976-2007, based on four sub-periods of seven years (1976-1983; 1984-1991; 1992-1999 and 2000-2007). These periods were related to the time prior and after the introduction of the orphan drug legislations in the USA (1983) and Europe (2000). In this thesis data was collected for only one complete period (1976-2008). It is not possible to predict the outcome range of the PubMed search strings in advance. The two categories of scientific output are therefore determined after data collection by dividing the cases of the control group into approximately two equal sub-groups based on the number of scientific publications in PubMed (based on Heemstra et al., 2009). As a result, the variable is measured by an ordinal scale.

Pharmaceutical formulation

This variable is operationalized by investigating the mode of administration of the first authorized OMP. Based on Heemstra et al. (2008a) it is expected that most authorized treatments either have an oral (e.g. tablet) or parenteral (e.g. injection or infusion) administration mode. As a result, this variable is measured by a nominal scale with two categories, namely parenteral and oral.

➢ 4.1.4 Disease-related characteristics (independent variables)

Disease class

The current version, as of August 2010, of the International Classification of Diseases (ICD) of the World Health Organization (WHO) is used to operationalize this variable (based on Heemstra et al., 2009). This classification is defined by the WHO as "the international standard diagnostic classification for all general epidemiological, many health management purposes and clinical use" (World Health Organization, 2010). Within this thesis, the same chapters of the ICD-10 version as used by Heemstra et al. (2009) are discerned in order to categorize the included rare indications (for a list of the included chapters see table 4.1). As a result, this variable has been operationalized by means of a nominal scale in this thesis.

Childhood disease

Heemstra et al. (2008a: 547) defined a rare indication as childhood disease when the "majority of the diagnosis is made before age 18". Orpha.net, on the other hand, uses five different categories for the age of onset of a rare disease: (1) neonatal/infancy; (2) childhood; (3) adolescence/young adulthood; (4) adulthood and (5) variable. In this thesis a rare indication has been recognized as childhood disease if the rare indication is included in the first or second category of Orpha.net. Furthermore, if the age of onset is variable according to Orpha.net, additional sources are consulted to assess whether the majority of onset is before or after age 18 (based on Heemstra, 2008a). As a result, the variable is measured in this thesis using a nominal scale of two categories, namely childhood and non-childhood (i.e. adulthood).

Inheritable disease

Heemstra et al. (2008a: 547) defined a rare indication as inheritable when "the majority of the cases is caused by genetic inheritance". Orpha.net, on the other hand, uses four categories for the inheritance of a rare indication: (1) autosomal dominant; (2) autosomal recessive; (3) x-linked recessive and (4) sporadic. Within this research a rare indication is recognized as inheritable if the disease is included in the first, second or third category of Orpha.net. As a result, this variable is measured by a nominal scale of two categories, namely inheritable and non-inheritable.

Chronic disease

In this thesis this variable is operationalized by the definition of Heemstra et al. (2008a). Heemstra et al. (2008a: 547) defined an orphan disease as chronic if the duration of the indication is generally over 3 months. As a result, this variable has a nominal scale with two categories, namely chronic and non-chronic.

In conclusion, the operationalization of the development of FOMP's (i.e. block one) is summarized in table 4.1:

Table 4.1: Operationalization of the variables – the development of FOMP's (block one)

Concept	Dimension	Indicator	Scale
Follow-on OMP (FOMP)		-authorized OMP having no FOMP -authorized OMP having at least one FOMP	nominal
Market-related characteristics	Prevalence	-< 0.1-0.9/100,000 -0.1-0.9/100,000 -1-9/100,000 -10-50/100,000	ordinal
	Turnover first authorized OMP	annual sales in million US dollar (categories have to be announced)	ordinal
	Other OD first authorized OMP	-other OD -no other OD	nominal
	Other approval first authorized OMP	-other approval -no other approval	nominal
Product-related characteristics	Disease-specific scientific output	number of publications in PubMed (categories have to be announced)	ordinal
	Formulation first authorized OMP	-parenteral -oral	nominal
Disease-related characteristics	Childhood	-childhood -non childhood (i.e. adulthood)	nominal
	Chronic	-chronic -non chronic	nominal
	Inheritable	-inheritable -non inheritable	nominal

Continuation table 4.1: Operationalization of the variables – the development of FOMP's (block one)

Concept	Dimension	Indicator		Scale
	Class	-A00-B99	infectious and parasitic diseases	nominal
		-C00-D48	oncological diseases	
		-D50-D89	diseases of the blood	
		-E00-E90	metabolic disorders	
		-F00-F99	mental and behavioral disorders	
		-G00-G99	nervous system diseases	
		-H00-H99	eye diseases	
		-I00-I99	circulation system diseases	
		-J00-J99	respiratory system diseases	
		-K00-K99	digestive system diseases	
		-L00-L99	diseases of the skin	
		-M00-M99	musculoskeletal system diseases	
		-P00-P99	conditions in the perinatal period	
		-Q00-Q99	congenital malformations	
		-S00-T98	injury and poisoning	
		-V	other diseases	

4.2 Characterization of the sponsors of FOMP's (block two)

➢ 4.2.1 Business-related characteristics of the sponsors of FOMP's

Please note that all business-related characteristics (i.e. experience, size, type and financials) have been measured at the end of the year in which the first OMP is approved, since this approval confirms the existing of a treatment for that rare indication. As a result, the sponsors of FOMP's have to base their subsequent decision regarding the development process on their available resources (e.g. employees, financials) of that moment.

Company's experience

Heemstra et al. (2008a) measured the experience of a company by three different indicators, namely the sponsor has (1) market authorization for other medicinal products; (2) other OD's and (3) other authorized OMP's. The authors (2008a: 545) concluded that "orphan drug approval was strongly associated with previous experience of the sponsor in obtaining approval for another orphan drug" (indicator (3): other authorized OMP's). Furthermore, Rzakhanov (2008) argued that having OD's does increase the market value of a company. Having exactly one OD does not increase the market value of a company, however, having more than one OD generates a higher market value. Consequently, this variable is operationalized in this thesis by two dimensions:

(1) a sponsor has anywhere in the world at least one other authorized OMP (ordinal scale);

(2) a sponsor has anywhere in the world other OD's; measured by two indicators: (1) ≤ 2 other OD's and (2) ≥ 2 other OD's (based on Rzakhanov, 2008) (ordinal scale).

Company's size

The company's size is measured by the number of employees working in the company and/or by the company's turnover (European Commission, 2010b). More detailed, the European Commission discerned three categories of enterprises in their SME definition: micro-; small- and medium-sized enterprises. In addition, a category of large-sized companies is available. However, in this thesis just two categories are discerned (i.e. an ordinal scale):

(1) SME companies having less than 250 employees or an annual turnover of less than 50 million euro;

(2) large-sized companies having more than 250 employees or an annual turnover of more than 50 million euro.

Company's type

Rzakhanov (2008) operationalized the diversification of a company by the number of therapeutic areas in which the firm is involved by means of the International Classification of Diseases (ICD) of the WHO. The author used a

calculation to decide whether a company was diversified or not. However, Rzakhanov (2008) did not explain how the outcome of his calculation (i.e. 1 – (therapeutic areas/total projects)) has to be interpreted. Consequently, this thesis decided to identify the firm as diversified if the sponsor is engaged in more than one therapeutic area, while the firm is classified as non-diversified if the sponsor focuses on just one therapeutic area. This variable has thus been measured by a nominal scale, namely diversified or non-diversified.

Company's financials

The financials of a company are measured by the annual turnover of the sponsor in million US dollar. However, it is not possible to predict the range of the turnover of the companies in advance. Consequently, the indicators are determined after data collection by dividing the cases of the control group into three equal sub-groups based on the annual turnover in million US dollars (based on Heemstra et al., 2009). As a result, this thesis operationalized this variable using an ordinal scale.

➢ 4.2.2 Decision of the sponsors of FOMP's to continue further development after approval of first OMP

Sponsors of FOMP's could decide to terminate or continue further development of their FOMP after the market authorization of the first OMP for the same rare disease. Nevertheless, it is important to clearly define the decision to prevent inconsistencies regarding continuation or termination in this thesis.

A sponsor continued further development if the market authorization of the first OMP was before the designation date of the FOMP, based on the Community Register of Orphan Medicinal Products. To assess the decision of the sponsors of FOMP's having a designation date prior to authorization of the first OMP, other sources in the public domain (e.g. sponsor's pipeline, annual reports, SEC-fillings, Clinicaltrial.gov, Google and press releases) were consulted. Based on all these information, the following two groups (i.e. a nominal scale) can be discerned in this thesis:

(1) sponsors of FOMP's that terminate further development after market authorization of the first OMP;

(2) sponsors of FOMP's that continue further development after market authorization of the first OMP.

➢ 4.2.3 Significant benefit as reason for decision FOMP sponsors

The concept of significant benefit is operationalized by means of the three categories (i.e. an improved efficacy, an improved safety or a major contribution to patient care) of the guideline of the EMA. Further elaboration of the three categories will be based on the available assumptions of significant benefit of the FOMP's. It is not possible to determine elaboration of the three categories in advance. Therefore, after data collection, all the assumptions are organized and thereafter classified in the most appropriate categories based on the EMA guideline (e.g. the assumption fewer side effects will be classified in the category improved safety).

In conclusion, the operationalization regarding the characterization of the sponsors of FOMP's (i.e. block two) is summarized in table 4.2:

Table 4.2: Operationalization of the variables – characterization of sponsors of FOMP's (block two)

Concept	Dimension	Indicator	Scale
Business-related characteristics	Company's experience		
	Other orphan designation	≤ 2 other OD's ≥ 2 other OD's	ordinal
	Other authorized OMP	no other authorized OMP at least one other authorized OMP	ordinal

Continuation table 4.2: Operationalization of the variables – characterization of sponsors of FOMP's (block two)

Concept	Dimension	Indicator	Scale
	Company's size	SME (≤ 250 employees) large (≥ 250 employees)	ordinal
	Company's type	non-diversified (one therapeutic area) diversified (more than one therapeutic area)	nominal
	Company's financials	annual turnover in million US dollar (categories have to be announced)	ordinal
Sponsor's decision		termination further development FOMP continuation further development FOMP	nominal
Significant benefit		improved efficacy improved safety major contribution to patient care (further elaboration has to be announced)	nominal

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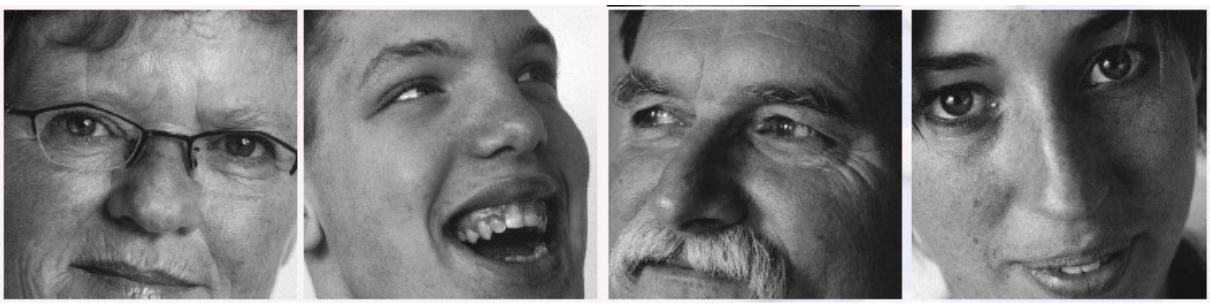
METHODOLOGY



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Chapter 5 – METHODOLOGY

This chapter elaborates the methodology of this thesis by describing the research design, the sample selection, the data collection and the data analysis respectively. The quality of the research is also discussed by means of the reliability and the validity (i.e. construct, internal and external validity).

5.1 Research design and sample selection

➢ 5.1.1 Research design

In this thesis quantitative as well as qualitative research is conducted. In quantitative research data is collected by standardized approaches on a range of variables to search for causal relationships between the dependent and the independent variables (Henn et al., 2006). The first block (i.e. the development of FOMP's) of this thesis consists of quantitative research due to the aim of explaining factors that cause the development of at least one FOMP for rare indications with an authorized OMP. Qualitative research, on the other hand, aims to get insight in underlying motives that people have for doing what they do (Henn et al., 2006). The qualitative part within this thesis is the analysis regarding to what extent, and for what reason, the FOMP sponsors decide to continue or terminate further development after market approval of the first OMP for the same rare disease.

➢ 5.1.2 Sample selection

All rare indications that obtained at least one authorized OMP for the treatment of that rare indication in Europe between 1 January 2001 and 31 December 2008 were enrolled in the sample of this thesis. Please note, authorized OMP's intended either for the diagnosis or prevention of a rare disease were excluded from the sample. The rare diseases with an authorized OMP are thereafter divided into two groups, as reflected in the operationalization:
(1) rare indications having an authorized OMP, and **no FOMP** (**control** group);
(2) rare indications having an authorized OMP, and **at least one FOMP** (**experimental** group).

The experimental group is further elaborated in this thesis to get insight in the second block of the stated research question. For each rare indication included in this group, all the FOMP's registered in the Community Register of Orphan Medicinal Products between 1 January 2001 and 30 April 2010 are enrolled in an additional sample. This additional sample is thereafter analyzed to further elucidate the characterization of the FOMP sponsors of the rare indications in the experimental group.

External validity

The external validity of the research explains to what extent the findings of the performed study are generalizable beyond the study field (Yin, 2003). This thesis only focuses on orphan drug development, and more detailed on FOMP development, in Europe. As a result, the findings and conclusions of this thesis are generalizable to orphan drug development, and FOMP development, on regional level (i.e. Europe).

5.2 Data collection

➢ 5.2.1 Data gathering

Sources in the public domain provided all the data with respect to this thesis. In general, the following sources are consulted: Community Register of Orphan Medicinal Products (http://ec.europa.eu/health/documents/community-register/html/orphreg.htm) (Europe), Orphan Product Drug designation database (http://www.accessdata.fda.gov/

scripts/opdlisting/oopd/index.cfm) (USA), websites of sponsors, documentation of sponsors (e.g. annual reports, financial reports and SEC-fillings (http://www.sec.gov/edgar/searchedgar/companysearch.html)), Summaries of Opinion (SofO), European Public Assessment Reports (EPAR), PubMed, Google, ICD-classification of the WHO, Orpha.net (2010b) and the report: prevalence of rare diseases (issue November 2009) (Orpha.net, 2009b). To be more detailed, data collection regarding both blocks is further elaborated in paragraph 5.2.2 and 5.2.3.

Construct validity

The concept of construct validity is related to the establishment of correct operational measures with regard to the variables investigated in the study (Yin, 2003). To deal with the concept, this thesis decided to operationalize most variables based on earlier research. Furthermore, part of the variables is operationalized by means of international used classifications, like the ICD-10 classification of the WHO for the variable disease class. Finally, in this thesis only data from sources in the public domain is collected to deal with the construct validity. It is assumed that data in the above mentioned public sources gives a good representation regarding the variables that are measured in this thesis (e.g. information, like financials and company size, in annual reports and SEC-fillings is audited).

➢ 5.2.2 Development of FOMP's (block one)

Market-related characteristics

The Orpha.net report (issue November 2009) is consulted in this thesis to examine the estimated prevalence of the included rare indications, because in Orpha.net report series all data is collected by carrying out multiple literature sources and in the same manner (Oprha.net, 2009b). In case the prevalence of a rare indication was not included in the Orpha.net report series, the website of Orpha.net was consulted. It is assumed that the prevalence data on this website is collected in the same way as the prevalence data in the report series. If no prevalence data was available in both sources, the European Public Assessment Report (EPAR) of the associated authorized OMP (e.g. EPAR of Glivec® for the indication chronic myeloid leukemia) was reviewed to assess the prevalence. Finally, a Summary of Opinion (SofO) was examined if the prevalence was not available in all these mentioned sources. The EPAR is assessed prior to the SofO, because the prevalence data in the EPAR (authorization report) is more recent than the prevalence data in the SofO (designation report). Nevertheless, sponsors are responsible for data in both the SofO and EPAR and consequently, the prevalence calculation methodology will vary and may differ from the Orpha.net methodology. To assess whether the first authorized OMP for a specific rare indication is also designated and/or authorized outside Europe, the Orphan Product Drug designation database of the FDA in the USA is consulted. To conclude, the annual turnover of the first authorized OMP is investigated by reviewing annual reports of sponsors that launched the first approved OMP's on the market.

Product-related characteristics

Information in the EPAR's of the first approved OMP's is used to collect data with respect to the pharmaceutical formulation. The disease-specific scientific output data is collected by search strings which are composed in Excel (e.g. "Lennox-Gastaut syndrome"[All Fields]) AND English[LA] AND (Journal article[PT] OR Case reports[PT] OR Technical report[PT]) NOT (Review[PT] OR Comment[PT] OR Letter[PT] OR Meta-analysis[PT]) AND ("1976/01/01"[PDAT] : "2008/12/31"[PDAT])). The composed search strings are thereafter run through PubMed to determine the number of scientific publications for each rare indication included in the sample.

Disease-related characteristics

The website of Orpha.net (2010b) was consulted to collect data with regard to the disease-related characteristics (e.g. disease class). In addition, this thesis examined sources in the public domain (e.g. PubMed or Google) if one of the variables of the included rare indications was not available in the database of Orpha.net (2010b).

➢ 5.2.3 Characterization of the sponsors of FOMP's (block two)

Business-related characteristics and decision of the sponsors of FOMP's

Most of the sponsor characteristics were available in public sources of the sponsors, like annual reports, financial reports, websites and SEC-fillings (i.e. 10-K forms that reflect a comprehensive overview of both the business and financial conditions of an US sponsor and that include the audited financial data (SEC, 2010)). Furthermore, also the database of Clinicaltrial.gov is consulted, which is constructed by the US National Institutes of Health (NIH) in collaboration with the FDA. This database contains data regarding more than 90,000 trials (Clinicaltrial.gov, 2010). As a result, Clinicaltrial.gov was valuable to find information concerning the phase of development of the FOMP's and thus with regard to the decision of sponsors of FOMP's to continue or terminate further development after market approval of the first OMP for the same rare disease.

Significant benefit as reason for decision FOMP sponsors

To collect data regarding the assumptions of significant benefit different sources in the public domain are used. First, EPARs are consulted for FOMP's that are successfully further developed and are **authorized as FOMP** for a rare disease yet. EPARs reflect the scientific conclusion of the CHMP and provide a summary of the reasons for the CHMP opinion regarding market authorization of an OMP (EMA, 2010a). In other words: an EPAR provides information regarding the significant benefit of a FOMP compared to earlier authorized OMP's for the same rare disease. The Summary of Opinion (SofO), on the other hand, reflects assumptions of significant benefit at the time of designation and compares the FOMP with existing treatments of that moment (i.e. the first approved OMP). As a result, a SofO can only be consulted if the FOMP obtained an OD **after the authorization** of the first OMP for the same rare disease. Sponsor documents, like annual reports and websites, are therefore consulted in this thesis if the FOMP obtained the OD **before the authorization** of the first OMP for the same rare indication. This thesis assumes that information regarding the potential of a FOMP has to be reflected in one these sponsor documents.

5.3 Data analysis

➢ 5.3.1 Development of FOMP's (block one)

Database construction

During the data collection phase, a database (Excel file) including all rare indications of the experimental (FOMP) and control (no FOMP) group was constructed (please note that this database, but also the other below mentioned databases, are available on the attached cd-rom of this thesis). The mentioned database contained the information with regard to all the variables of the market-related, product-related and disease-related characteristics. After data completion, the data was divided among the right indicator of the operationalization (e.g. a disease prevalence of 6/100,000 belongs to the indicator 1-9/100,000). Moreover, for some independent variables (e.g. disease-specific scientific output) categories have been determined by dividing the control group into approximately two or three equal groups with regard to the number of cases, as reflected in chapter 4. Finally, with respect to the disease class this thesis decided to use only two indicators (C00-D48 (oncologic disorders) vs. other disorders) instead of all the

ICD-10 classes of the operationalization, due to the low number of rare indications in the other ICD-10 classes. To conclude, all collected data is used to elaborate absolute frequencies and percentages regarding the dimensions of the market-related, product-related and disease-related characteristics (descriptive statistics).

Method of analysis

Subsequently, the database is quantitatively analyzed based on Heemstra et al. (2008a and 2009). More detailed, the market-related, product-related and disease-related characteristics of the experimental and control group were compared by means of univariate logistic regression analyses. Odds ratios (OR) and 95 % confidence intervals (CI) are calculated for all the variables of the conceptual model. In general, a logistic regression aims to predict whether an event will happen or not and moreover, to identify the variables playing a role in such a prediction (De Pelsmacker and Van Kenhove, 2006: 285). However, only binary independent variables can be regressed against the dependent variable in such logistic regression. As a result, some variables (e.g. pharmaceutical formulation) has been translated into dummy variables implying that for each variable one indicator obtains the value 0 (i.e. the reference category) (e.g. regarding the pharmaceutical formulation the indicator oral obtained the value 1 and the indicator parenteral obtained the value 0 in this thesis).

In a second step, a multivariate model was used to test whether the independent variables are mutually related. In this model the independent variables of the univariate analyses with statistically significant OR's (p-value < 0.05) were compared using a backward logistic regression procedure (Heemstra et al., 2008a). To test the validity of this multivariate model the R^2 value is commonly used, indicating the percentage of the variance of the dependent variable that is explained by the proposed model. More detailed, a high percentage implies that the model seems to be a good representation for factors influencing the dependent variable (UCLA Academic Technology Services, 2010). Because no equivalent to the R^2 value is available for a logistic regression, some 'pseudo' R^2 values are constructed. These values are ranged between zero and one and a value close(r) to one implies a better fitting of the proposed model (UCLA Academic Technology Services, 2010). More detailed, in this research the pseudo R^2 value approach by Nagelkerke is performed, which is one of the most commonly reported R^2 squares (based on Van den Berg et al., 2009). Finally, the percentage of the dependent variable that is correctly predicted is also applied in order to verify the validity of the multivariate model (UCLA Academic Technology Services, 2010).

Internal validity

The R^2 square and the correctly predicted percentage of the dependent variable give insight in the internal validity of this thesis. The internal validity of a research is related to the establishment of causal relationships. A research has a good internal validity if the outcome can be attributed to the investigated variables and not to possible other unforeseen factors (Yin, 2003). High values for the R^2 square as well as the correctly predicted percentage of the dependent variable imply therefore a better internal validity for the results of this thesis.

➢ 5.3.2 Characterization of the sponsors of FOMP's (block two)

Database construction

Regarding the characterization of the sponsors of the FOMP's, a second database (Excel file) is constructed that included all FOMP's of the rare indications in the experimental group. This database contained data with respect to the characteristics of the sponsors of FOMP's. Comparable to the first database, after data completion, all data is divided among the correct indicators of the operationalization (e.g. 653 employees implies that a sponsor is a large-sized company). Furthermore, for some variables categories were determined by dividing the control group

into two or three approximately equal groups regarding the number of cases, as reflected in the operationalization chapter. To conclude, a third database (Excel file) has been established for the expected assumptions of significant benefit of the FOMP's.

Method of analysis

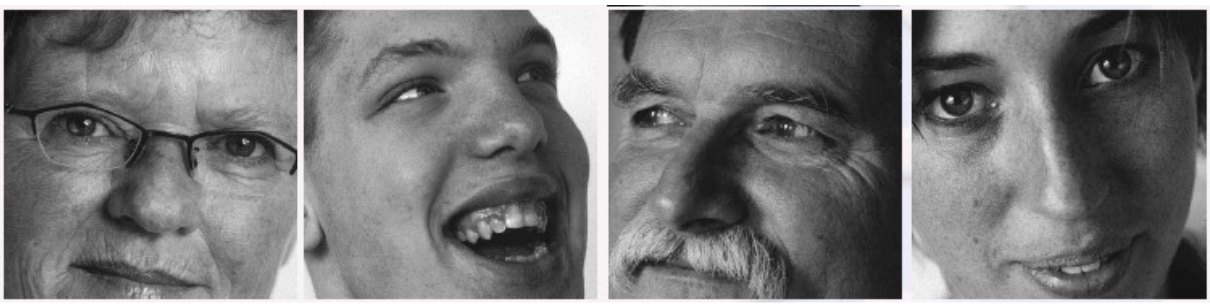
After data completion, all collected assumptions of significant benefit were compared and mapped by means of some key words of the EMA guideline (e.g. mechanism of action, tolerability and side effects). As a result, some more detailed classes for each main category (i.e. improved efficacy, improved safety and major contribution to patient care) could be identified. Furthermore, the assumptions of significant benefit were categorized per disease class (C00-D48 vs. other ICD-10 classes). Finally, all information of the databases was used to elaborate absolute frequencies and percentages (descriptive statistics) regarding the characterization of the sponsors of FOMP's.

5.4 Reliability of this thesis

The previous paragraphs described the used methodology of the research to deal with the reliability of this thesis. A study is reliable if other researchers can repeat the conducted study with getting the same findings (Yin, 2003). All performed steps (i.e. sample selection, data collection and data analysis, but also the operationalization) of this thesis are therefore described in a detailed way. As a result, researchers are able to follow the same procedure as done in this thesis to get the same results and conclusions. All studies are also conducted by one researcher (Anne Brabers) to increase the reliability of this thesis.

(copied from Stuurgroep Weesgeneesmiddelen, 2010a)

RESULTS



(copied from Stuurgroep Weesgeneesmiddelen, 2010a)

Chapter 6 – RESULTS

In this chapter the main results of the performed studies of this thesis are presented. First, the results regarding the factors explaining the development of FOMP's are reflected in paragraph 6.1. Thereafter, the characteristics of the sponsors of FOMP's are presented in paragraph 6.2.

6.1 Development of FOMP's (block one)

The first sub-question aimed to investigate to what extent rare indications with an authorized OMP have at least one FOMP. It has been observed that from the beginning of the EODR (2000) up to 31 December 2008 48 OMP's intended for the treatment of a rare indication obtained market authorization from the CHMP (based on data from Orpha.net, 2009a). Most of these approved OMP's are for the treatment of one rare indication. However, some of the products (e.g. Glivec® and Sprycel®) are approved for more than one orphan disease, resulting in a total of 58 authorized orphan indications in Europe up to and including 31 December 2008. More specific, the 58 approved OMP's are launched on the market for the treatment of 44 different rare indications.

In appendix II an extended overview of the included rare diseases, their related authorized OMP and whether the rare indication is included in the experimental or control group is given. To summarize, 26 of the 44 (59.1 %) rare indications with an approved OMP in Europe have at least one FOMP and are included in the experimental group. Consequently, 18 of the 44 (40.9 %) rare indications with an authorized OMP in Europe did not have at least one FOMP and are included in the control group.

The second sub-question aimed to identify factors that explain why some rare indications with an authorized OMP have at least one FOMP compared to other rare indications with an authorized OMP and no FOMP. As a result, the experimental and control group were compared for market-, product- and disease-related characteristics. The result of the descriptive statistics, univariate analyses and multivariate analysis are presented hereafter.

➢ 6.1.1 Descriptive statistics (see table 6.1 on the next page)

Market-related characteristics

Approximately three quarter (70.3 %) of the first authorized OMP's have annual sales of more than 50 million US dollar. Moreover, around 80 % of the first approved OMP's are also designated outside Europe, in addition, also three quarter (75.0 %) of them received a market authorization outside Europe. Furthermore, 79.1 % of the orphan diseases have a prevalence above 1 patient per 100,000 inhabitants. However, none of the rare indications in the experimental group has a prevalence of either < 0.1/100,000 or 0.1-0.9/100,000. While, on the other hand, in the control group approximately half (52.9 %) of the rare indications have a prevalence in one of these 2 categories.

Product-related characteristics

With respect to the pharmaceutical formulation of the first approved OMP's, it is observed that 54.5 % of the first authorized OMP's has an oral administration mode. In addition, approximately three quarter (77.3 %) of the rare indications have more than 450 scientific publications in PubMed.

Disease-related characteristics

More than one third (34.1 %) of the rare indications having an authorized OMP belong to the class of oncologic disorders (i.e. C00-D48). However, further detailed, 11.1 % and 50.0 % of the orphan diseases in the control and

experimental group, respectively, belong to the oncology class (i.e. C00-D48). Furthermore, with respect to the age of onset of the rare indications it is observed that in general 43.6 % of the indications with an authorized OMP is a childhood disease. More specific, in the experimental group 29.2 % of the rare diseases have an age of onset in childhood, while in the control group 66.7 % of the indications has an age of onset in childhood. To conclude, the majority of the included rare indications are chronic and not inheritable (87.2 % and 63.6 % respectively).

Table 6.1: Results univariate analyses (Europe)

Concept and Dimension	Indicators	Total (N = 44) (%)		Experimental group (N = 26) (%)		Control group (N = 18) (%)		OR (95 % CI)
MARKET-RELATED								
Prevalence(*)	< 0.1/100,000	4	(9.3 %)	0	(0.0 %)	4	(23.5 %)	not applicable
	0.1-0.9/100,000	5	(11.6 %)	0	(0.0 %)	5	(29.4 %)	not applicable
	1-9/100,000	16	(37.2 %)	14	(53.8 %)	2	(11.8 %)	reference level
	10-50/100,000	18	(41.9 %)	12	(46.2 %)	6	(35.3 %)	0.3 (0.0 – 1.7)
Prevalence(*) (2-category)	< 1/100,000	10	(23.3 %)	1	(3.8 %)	9	(52.9 %)	reference level
	> 1/100,000	33	(76.7 %)	25	(96.2 %)	8	(47.1 %)	28.1 (3.1 – 257.4)
Turnover first authorized OMP(*)	< 50 million US $	11	(29.7 %)	4	(17.4 %)	7	(50.0 %)	reference level
	> 50 million US $	26	(70.3 %)	19	(82.6 %)	7	(50.0 %)	4.8 (1.1 – 21.4)
First OMP designated outside Europe	no	8	(18.2 %)	5	(19.2 %)	3	(16.7 %)	reference level
	yes	36	(81.8 %)	21	(80.8 %)	15	(83.3 %)	0.8 (0.2 – 4.1)
First OMP approved outside Europe	no	11	(25.0 %)	7	(26.9 %)	4	(22.2 %)	reference level
	yes	33	(75.0 %)	19	(73.1 %)	14	(77.8 %)	0.8 (0.2 – 3.2)
PRODUCT-RELATED								
Formulation	parenteral	20	(45.5 %)	9	(34.6 %)	11	(61.1 %)	reference level
	oral	24	(54.5 %)	17	(65.4 %)	7	(38.9 %)	3.0 (0.9 – 10.3)
Scientific output	< 450 publications	10	(22.7 %)	1	(3.8 %)	9	(50.0 %)	reference level
	> 450 publications	34	(77.3 %)	25	(96.2 %)	9	(50.0 %)	25.0 (2.8 – 226.1)
DISEASE-RELATED								
Class	other class	29	(65.9 %)	13	(50.0 %)	16	(88.9 %)	reference level
	C00-D48	15	(34.1 %)	13	(50.0 %)	2	(11.1 %)	8.0 (1.5 – 42.0)
Childhood(*)	adulthood	22	(56.4 %)	17	(70.8 %)	5	(33.3 %)	reference level
	childhood	17	(43.6 %)	7	(29.2 %)	10	(66.7 %)	0.2 (0.1 – 0.8)
Chronic(*)	non chronic	5	(12.8 %)	3	(13.6 %)	2	(11.8 %)	reference level
	chronic	34	(87.2 %)	19	(86.4 %)	15	(88.2 %)	0.8 (0.1 – 5.7)
Inheritable	non inheritable	28	(63.6 %)	18	(69.2 %)	10	(55.6 %)	reference level
	inheritable	16	(36.4 %)	8	(30.8 %)	8	(44.4 %)	0.6 (0.2 – 1.9)

(*) Percentage prevalence is based on N = 43, 26 and 17 respectively
(*) Percentage turnover first authorized OMP is based on N = 37, 23 and 14 respectively
(*) Percentage childhood is based on N = 39, 24 and 15 respectively
(*) Percentage chronic is based on N = 39, 22 and 17 respectively

➢ 6.1.2 Univariate analyses

Besides the descriptive statistics, also the results of all the univariate analyses are depicted in table 6.1. For some variables statistically significant relations were observed. However, the association was strongest for the scientific output for a specific disease. More detailed, orphan diseases with more than 450 scientific publications in PubMed have a 25.0-fold increase in the chance to obtain at least one FOMP compared to rare indications having less than 450 scientific publications in PubMed (OR = 25.0; CI = 2.8-226.1).

Furthermore, the results show that oncologic disorders with a first approved OMP have a 8-fold increased odds to obtain at least one FOMP in comparison with rare diseases in other ICD-10 classes (OR = 8.0; CI = 1.5-42.0). In addition, a statistically significant relation was observed for another disease-related characteristic, namely the age of onset of the disease (i.e. childhood). Rare indications having an age of onset in childhood have a 5-fold lower chance to obtain at least one FOMP than indications with an age of onset in adulthood (OR = 0.2; CI = 0.1-0.8). Moreover, a statistically significant association was found for the annual turnover of the first approved OMP. Rare diseases having a first authorized OMP with more than 50 million US dollar sales annually have an almost 5-fold higher probability on FOMP's than rare diseases having a first approved OMP with annual sales below 50 million US dollar (OR = 4.8; CI = 1.1-21.4).

For the disease prevalence (see table 6.1) the descriptive statistics show that none of the rare diseases included in the experimental group had a prevalence below 1 patient per 100,000 inhabitants, consequently no OR's could be calculated. Nevertheless, the descriptive statistics indicate a strong association between the disease prevalence and the likelihood to obtain at least one FOMP. As a result, an additional univariate analysis is performed by dividing the rare diseases in two categories, namely < 1/100,000 (category 1 and 2 of table 6.1) and > 1/100,000 (category 3 and 4 of table 6.1). This distinction is based on the fact that all 26 rare indications in the experimental group had a prevalence above 1 per 100,000, while the rare indications in the control group are approximately equal divided between the categories. Moreover, one rare indication of the experimental group is included in the first category (< 1/100,000) to be able to perform the additional univariate analysis. Indeed, this surrogate analysis confirmed a strong statistically significant relation. Rare indications with an approved OMP and a prevalence above 1/100,000 have an almost 30-fold higher odds on FOMP's than rare diseases with less than 1 patient per 100,000 inhabitants (OR = 28.1; CI = 3.1-257.4).

➢ 6.2.3 Multivariate analysis

As a second step, a multivariate analysis was performed, including all the variables with statistically significant associations (p value < 0.05). Table 6.2 depicts the results of this multivariate analysis. The final model showed one characteristic as predictor for the chance to obtain at least one FOMP for rare disease with an approved OMP, namely the disease prevalence (OR = 25.2; CI = 2.5-259.2). The pseudo R^2 value of the final model was 0.388, which implies that 38.8 % of the dependent's variance has been explained. Furthermore, the overall percentage of correctly predicted values of the dependent variable was 81.8 % (both tables are presented in appendix III).

Table 6.2: Results multivariate analysis (Europe)

Dimension	Indicator	OR[1] (95 % CI)
Prevalence	< 1/100,000	reference level
	> 1/100,000	25.2 (2.5 – 259.2)

(1) Adjusted for significant variables of the univariate analysis of table 6.1. Variables in table 6.2 are those that remained in the multivariate analysis after a backward LR procedure.

➢ 6.2.4 Development of FOMP's in the USA

Although this thesis is not focused on the USA, some first preliminary work with regard to factors explaining the development of FOMP's in the USA is done in this thesis. The findings of these US analyses are shortly described hereafter, however, a more extensive overview regarding the US sample is presented in appendix IV of this thesis. The US sample included 71 rare indications, from which 38 (53.5 %) and 33 (46.5 %) rare diseases were included in the experimental and control group respectively. In line with the European sample, both groups were compared

on different characteristics. However, only the statistically significant characteristics of the univariate analyses of the European sample were included in the US study (disease prevalence, disease-specific scientific output, disease class, age of onset and turnover first approved OMP), because of practical limitations (i.e. time).

Table 6.3 presents the results of the descriptive statistics and the univariate analyses of the USA (for a discussion regarding the descriptive statistics, see appendix IV). For three included variables statistically significant relations were observed, namely disease class, disease prevalence and disease-specific scientific output. More detailed, the results show that oncologic disorders with a first approved OMP have a 10-fold increased chance to obtain at least one FOMP compared to rare indications in other ICD-10 classes (OR = 10.1; CI = 2.1-48.6). In addition, also rare indications with an authorized OMP and a prevalence above 1/100,000 have a 10-fold higher chance on FOMP's than rare indications with a prevalence below 1/100,000 (OR = 10.0; CI = 2.0-50.8). Finally, rare diseases with more than 655 scientific publications in PubMed have a more than 4-fold increase in the likelihood to obtain at least one FOMP than rare diseases with less than 655 scientific publications in PubMed (OR = 4.2; CI = 1.4-12.1).

Table 6.3: Results univariate analyses (USA)

Dimension	Indicator	Total (N = 71) (%)		Experimental group (N = 38) (%)		Control group (N = 33) (%)		OR (95 % CI)
Class	other class	54	(76.1 %)	23	(60.5 %)	31	(93.9 %)	reference level
	C00-D48	17	(23.9 %)	15	(39.5 %)	2	(6.1 %)	10.1 (2.1 – 48.6)
Prevalence 2 categories(*)	< 1/100,000	12	(19.0 %)	2	(5.6 %)	10	(37.0 %)	reference level
	> 1/100,000	51	(81.0 %)	34	(94.4 %)	17	(63.0 %)	10.0 (2.0 – 50.8)
Scientific output	< 655 publications	23	(32.4 %)	7	(18.4 %)	16	(48.5 %)	reference level
	> 655 publications	48	(67.6 %)	31	(81.6 %)	17	(51.5 %)	4.2 (1.4 – 12.1)
Childhood(*)	adulthood	34	(58.6 %)	21	(65.6 %)	13	(50.0 %)	reference level
	childhood	24	(41.4 %)	11	(34.4 %)	13	(50.0 %)	0.5 (0.2 – 1.5)
Turnover first authorized OMP(*)	< 175 million US $	25	(46.3 %)	14	(43.8 %)	11	(50.0 %)	reference level
	> 175 million US $	29	(53.7 %)	18	(56.2 %)	11	(50.0 %)	1.3 (0.4 – 3.8)

(*) Percentage prevalence is based on N = 63, 36 and 27 respectively
(*) Percentage childhood is based on N = 58, 32 and 26 respectively
(*) Percentage turnover first authorized OMP is based on N = 54, 32 and 22 respectively

Thereafter, also a multivariate analysis was performed, from which the results are depicted in table 6.4. The final model showed two characteristics as predictor for the chance to obtain at least one FOMP as rare indication with an authorized OMP, namely the disease prevalence and disease class (OR = 6.3; CI = 1.2-33.4 and OR = 5.9; CI = 1.2-30.0). The pseudo R^2 value of the model was 0.305, implying that 30.5 % of the dependent's variance has been explained. Moreover, the overall percentage of correctly predicted values of the dependent variable was 69.8 % (for both tables see appendix IV).

Table 6.4: Results multivariate analysis (USA)

Dimension	Indicator	OR[1] (95 % CI)
Prevalence	< 1/100,000	reference level
	> 1/100,000	6.3 (1.2 – 33.4)
Class	other class	reference level
	C00-D48	5.9 (1.2 – 30.0)

(1) Adjusted for significant variables of the univariate analysis of table 6.3. Variables in table 6.4 are those that remained in the multivariate analysis after a backward LR procedure.

6.2 Characterization of the sponsors of FOMP's (block two)

Sub-question three aimed to identify the number of FOMP's for each rare indication with an authorized OMP and at least one FOMP. A closer look to the 26 rare indications in the experimental group revealed that the indications in Europe obtained a total of 163 OD's between 1 January 2001 and April 2010 based on the Community Register of Orphan Medicinal Products. More detailed, figure 6.1 depicts the OD's of each rare indication included in the experimental group.

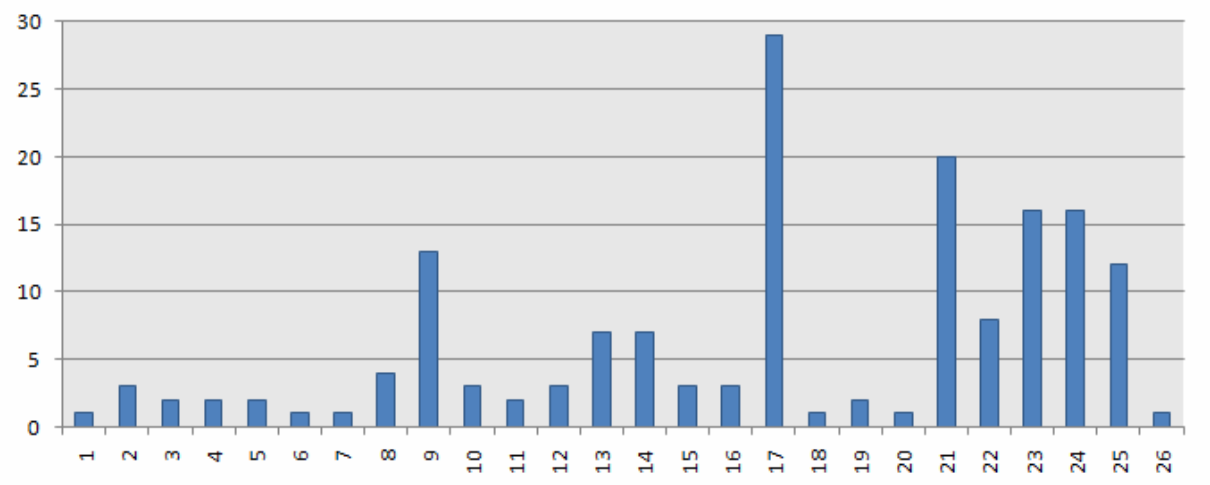


Figure 6.1: OD's per rare indication in the experimental group (N = 163) (Europe) (based on European Commission, 2010a)
(1 = Fabry disease, 2 = Angioedema, 3 = Acromegaly, 4 = Familial adenomatous polyposis, 5 = Wilson's disease, 6 = Hairy cell leukemia, 7 = Narcolepsy-cataplexy, 8 = Systemic sclerosis, 9 = Hepatocellular carcinoma, 10 = Gaucher disease, 11 = Acute promyelocytic leukemia, 12 = Gastrointestinal stromal tumor, 13 = Soft tissue sarcoma, 14 = Chronic myeloid leukemia, 15 = Hyperphenylalaninaemia, 16 = Sickle cell disease, 17 = Acute myeloid leukemia, 18 = Pompe disease, 19 = Chronic iron overload, 20 = Idiopathic hypereosinophilic syndrome, 21 = Renal cell carcinoma, 22 = Myelodysplastic syndrome, 23 = Multiple myeloma, 24 = Acute Lymphoblastic Leukemia, 25 = Pulmonary arterial hypertension, 26 = Adrenal cortical carcinoma)

A further analysis of the 163 OD's revealed that the development of 13 OD's (8.0 %) has been terminated before the approval of the first OMP for the same rare indication. In addition, 1 OD was intended for the diagnosis rather than for the treatment of a rare disease. As a result, 149 OD's remained in the European sample. From these 149 OD's, 120 OD's (80.5 %) were identified as being under development at or after authorization of the first OMP. Consequently, these 120 OD's are identified in this thesis as FOMP. Moreover, 16 (13.3 %) of these 120 FOMP's obtained a market authorization for one of the 26 included rare indications in the period 1 January 2001 to April 2010. Despite an in depth search into multiple sources in the public domain, for the remaining 29 OD's (19.5 %) we were unable to determine whether these OD's were still under development at or after the approval of the first OMP for the same rare disease. One explanation is that the sponsor of the OD is a consultancy company (n = 14) and as a result, no information was available in the public domain. To summarize, a sample of 120 FOMP's for 26 different rare indications was analyzed in this thesis.

➢ 6.2.1 Business-related characteristics of the sponsors of FOMP's

Sub-question 4 aimed to identify the characteristics of the sponsors of these 120 FOMP's, which are presented in table 6.5 on the next page. More detailed, two groups of FOMP's are discerned to explore the characteristics with regard to successful FOMP development (i.e. market approval for a FOMP).

(1)FOMP's that were under development at or after approval of the first OMP, and have not obtained market authorization yet (n = 104; **control group**);

(2)FOMP's that were under development at or after approval of the first OMP, but subsequently obtained market authorization (n = 16; **experimental group**).

Descriptive statistics (see table 6.5)

It is observed regarding the experience that more than half (53.3 %) of the sponsors had at least two other OD's either in Europe or the USA. Regarding the authorized FOMP's, it is observed that almost all (93.7 %) of these sponsors had at least 2 other OD's. Moreover, 15 of the 16 sponsors in this group had at least one other approved OMP, while in the control group more than 70 % of the sponsors did not have another authorized OMP at moment of authorization of the first OMP. Approximately half (46.4 %) of the sponsors are a large company, moreover, almost all (93.7 %) authorized FOMP's are launched on the market by sponsors with more than 250 employees. In addition, around 45 % of the sponsors had an annual turnover of more than 400 million US dollar. With respect to the type of the company it is observed that 33.6 % of the sponsors focus on just one therapeutic area (i.e. non-diversified). However, all authorized FOMP's are launched on the market by non-diversified sponsors.

Table 6.5: Business-related characteristics of sponsors of FOMP's

Business-related characteristic	Indicator	Total FOMP's (N = 120) (%)		Experimental (N = 16) (%)		Control (N = 104) (%)	
Experience							
Other orphan designation	≤ 2 other OD's	56	(46.7 %)	1	(6.3 %)	55	(52.9 %)
	≥ 2 other OD's	64	(53.3 %)	15	(93.7 %)	49	(47.1 %)
Other authorized OMP	no	76	(63.3 %)	1	(6.3 %)	75	(72.1 %)
	yes	44	(36.7 %)	15	(93.7 %)	29	(27.9 %)
Size(*)	SME	60	(53.6 %)	1	(6.3 %)	59	(61.5 %)
	large	52	(46.4 %)	15	(93.7 %)	37	(38.5 %)
Type(*)	non-diversified	40	(33.6 %)	0	(0.0 %)	40	(38.8 %)
	diversified	79	(66.4 %)	16	(100.0 %)	63	(61.2%)
Financials(*)	< 4,500	25	(27.5 %)	0	(0.0 %)	25	(33.3 %)
(in 1,000 US dollar)	4,500-400,000	26	(28.6 %)	1	(6.3 %)	25	(33.3 %)
	>400,000	40	(43.9 %)	15	(93.7 %)	25	(33.4 %)

(*) Percentage size is based on N = 112, 16 and 96 respectively
(*) Percentage type is based on n = 119, 16 and 103 respectively
(*) Percentage financials is based on N = 91, 16 and 75 respectively

➢ 6.2.2 Decision of the sponsors of FOMP's to continue further development after approval of first OMP

Sub-question 5 aimed to analyze to what extent the sponsors of the 120 FOMP's decided to terminate or continue further development after market approval of the first OMP for the same rare indication, and why.

From the data **only one FOMP** was identified for which development is most likely being terminated because of the authorization of the first OMP for the same orphan disease. The story of this FOMP (EU/3/07/482), PI-88 of the Australian company Progen, is reflected in box II of this thesis on the next page. Nevertheless, the analysis in general showed that all sponsors continued further development after market authorization of the first OMP for the same rare indication. As a result, it was decided to analyze a sample of FOMP's from the USA to confirm the positive decision of the European sample. The US sample contained 178 FOMP's, however, also all sponsors of these 178 FOMP's decided to continue further development after the market authorization of the first OMP for the same rare disease (a more detailed overview of this sample of the USA is reflected in appendix V of this thesis). Although the US sample verified the positive decision, it is not assumed that all FOMP's will be authorized and launched on the market in the near future. Joppi et al. (2006) examined that only 7.1 % of the OD's in Europe obtained market authorization.

BOX II – TERMINATION DEVELOPMENT PI-88 DUE TO TRIAL NEXAVAR®

➢ **Hepatocellular carcinoma**

Hepatocellular carcinoma, a type of primary liver tumor, is one of the most common malignances worldwide (Finn, 2010; Summary of Opinion PI-88, 2007). Nevertheless, hepatocellular carcinoma is an orphan disease, having an estimated prevalence of 9 patients per 100,000 inhabitants (Orpha.net, 2009b). Factors known to be related to the disease are viral hepatitis (B and C), alcohol-induced liver cirrhosis and metabolic diseases (e.g. diabetes) (Finn, 2010; Summary of Opinion PI-88, 2007). Possible treatments of hepatocellular carcinoma depend, among others, especially on the stage of development of the disease and include surgery, radiation therapy, chemotherapy or immunotherapy (Summary of Opinion PI-88, 2007).

➢ **Nexavar®**

Nexavar®, developed and marketed under collaboration of Bayer and Onyx, was authorized in 2007 by both the FDA (November) and the EMA (October) for the treatment of unresectable hepatocellular carcinoma. The authorization was based on a placebo-controlled phase III trial demonstrating a median overall survival for Nexavar-treated patients of 10.7 months (vs. 7.9 placebo) (Llovet et al., 2008). Nexavar® was the first systemic therapy prolonging survival of patients with advanced hepatocellular carcinoma and represented a breakthrough in the management of this rare disease (Mendizabal and Reddy, 2009).

➢ **PI-88**

The Australian based company Progen developed together with the Australian National University the compound PI-88 for, among others, hepatocellular carcinoma (Progen annual report 2002). A phase II study for hepatocellular carcinoma (post surgery) with three arms (2 doses PI-88 and 1 control) was commenced in July 2004 by the company. During the years 2005 and 2006, Progen further conducted their phase II study (Progen annual report 2004-2006). In 2007 positive results of the first stage of the phase II trial in patients who have undergone surgical removal were presented by the company (Progen annual report 2007). Based on these results, Progen wanted to initiate an international phase III study in the second half of 2007 (Progen annual report 2007). Moreover, on 14th of September 2007 Progen received an orphan designation (OD) (EU/3/07/482) for PI-88 for the treatment of hepatocellular carcinoma from the EMA.

➢ **Termination development PI-88**

Although Progen started their international phase III trial (i.e. PATHWAY study), the board of the company decided to terminate the PATHWAY trial on the 23th of July 2008 (Progen annual report 2008). The decision of the board was mainly based on competitive pressures in Europe and North America. Bayer and Onyx announced to launch a Nexavar® trial in patients who have received surgical resection (Progen, 2009). Consequently, the board of Progen was not convinced that PI-88 would be efficiently and cost-effectively through a global market launch (Progen, 2009). However, as of April 2010, Progen has partnered PI-88 and decided to further develop PI-88 for the Asian markets (Progen annual report 2009).

Moreover, Bayer and Onyx indeed launched in August 2008 their phase III trial (i.e. STORM study) for hepatocellular patients following surgery or local radiation (Onyx, 2010a). As of April 2010, the STORM study is ongoing and still recruiting patients (trial: NCT00692770) (see www.clinicaltrial.gov).

In an additional analysis it was explored whether the FOMP's are still under development yet (April 2010). And if not, why the development of the FOMP was terminated during the years between the market authorization of the first OMP and April 2010. The European and the US sample were included in the analysis, because of the few sponsors that decided to terminate development. Sponsors of 15 (12.6 %) of the 119 FOMP's in Europe decided to terminate development as of April 2010. Moreover, the development of 20 (11.2 %) of the 178 FOMP's in the USA has been terminated yet. Combining both samples resulted in development termination of 35 (11.8 %) of the 297 FOMP's. Furthermore, the development of 4 FOMP's stopped because of two different reasons, resulting in a database of 39 termination reasons.

In most (38.5 %) of the cases, the decision to terminate further development was related to clinical trials. On the one hand, because it was difficult to enroll patients (n = 5), on the other hand because of the results of the clinical trials (n = 10). Other termination reasons were failure of the registration process (20.5 %) and focusing on another more promising indication of the same OMP (12.8 %). Moreover, the development of 10.3 % of the FOMP's was terminated because of funding reasons. To conclude, for several FOMP's (n = 6) the reason to terminate further development was not found in sources of the public domain.

➢ 6.2.3 Significant benefit as reason for decision FOMP sponsors

To conclude, the 119 sponsors that further developed their FOMP after the market authorization of the first OMP for the same rare disease have to demonstrate significant benefit of their FOMP compared to this first authorized OMP. Because, without justifying significant benefit it is not possible to obtain market authorization for a FOMP in Europe from the EMA.

Assumptions of significant benefit

Regarding 13 FOMP's (10.9 %) no assumptions of significant benefit were identified, predominantly because no information was available in the mentioned sponsor documents (see 5.2 data collection) for FOMP's that obtained an OD before the market approval of the first OMP (n = 10). On the other hand, for several FOMP's (n = 3) the Summary of Opinion did not provide clear information regarding the assumption of significant benefit (e.g. "the product might be of potential significant benefit" (EU/3/06/409)). Nevertheless, assumptions were found for the other 106 (89.1 %) FOMP's in either the Summary of Opinion or in the mentioned sponsor documents (see 5.2 data collection). More detailed, for some (n = 22) of the FOMP's more than one assumption of significant benefit was observed. Resulting in a database that contained a total of 130 different assumptions, categorized by means of the EMA guideline as depicted in table 6.6 on the next page.

Most (84.7 %; n = 110) assumptions of significant benefit are related to the concept of improved efficacy. Within this category, most sponsors expect that their FOMP will be of significant benefit due to a different mechanism of action. Moreover, around one fifth (20.8 %) of the FOMP's is assumed to be of benefit because of treatment of a sub-group of patients (e.g. "FLT-3 mutated acute myeloid leukemia patients" (EU/3/06/389) or "patients who are resistant or intolerant to prior therapy including imatinib mesilate" (EU/3/05/339)). On the other hand, just 6.8 % (n = 9) of the FOMP's are expected to show an improved safety profile compared to the first authorized OMP for the same rare indication. More detailed, three classes of assumptions, fewer side effects, increased tolerability and improved safety (unspecified), were recognized in the database. However, more than half (55.6 %) of the FOMP's in this category are expected to have fewer side effects compared to existing treatments. To conclude, with regard to the contribution to patient care it is observed that, except for one FOMP, all assumptions were related to the

mode of administration (e.g. “it is a liquid form of 6-thioguanine, which could be given to children who have difficulty swallowing tablets” (EU/3/09/694) or “it is a new formulation that is given less often than conventional forms of the medicine” (EU/3/08/569)).

Table 6.6: Classes of assumptions of significant benefit

Category of significant benefit	Classes of significant benefit	Assumptions N =130 (%)	
Improved efficacy	Different mechanism of action	47	(36.2 %)
	Sub-group (including patients who do not respond on current treatments)	27	(20.8 %)
	Alternative/additional treatment	14	(10.8 %)
	Improve the long-term outcome of the patient	12	(9.2 %)
	More effective (unspecified)	10	(7.7 %)
	total	**110**	**(84.7 %)**
Improved safety	Fewer side effects	5	(3.8 %)
	Increased tolerability	2	(1.5 %)
	Improved safety (unspecified)	2	(1.5 %)
	total	**9**	**(6.8 %)**
Contribution to patient care	Mode of administration	9	(6.9 %)
	Wider availability	1	(0.8 %)
	total	**10**	**(7.7 %)**
General	Improve the treatment (unspecified)	1	(0.8 %)
	total	**1**	**(0.8 %)**

After getting more insight in the assumptions of significant benefit, 105 FOMP’s were divided into the three main categories, as depicted in table 6.7 (please note that one FOMP is excluded from the analysis, because this FOMP expects to improve the treatment in general. Moreover, it is possible that a FOMP is categorized in one category (improved safety), although more assumptions (fewer side effects, increased tolerability) are noticed in table 6.4. So, the actual number decreased to 117). Finally, figure 6.2 reflects the number of categories of significant benefit per FOMP.

Table 6.7: Categories of significant benefit

Category of significant benefit	Categories N =117 (%)	
Improved efficacy	98	(83.7 %)
Improved safety	9	(7.7 %)
Major contribution to patient care	10	(8.6 %)

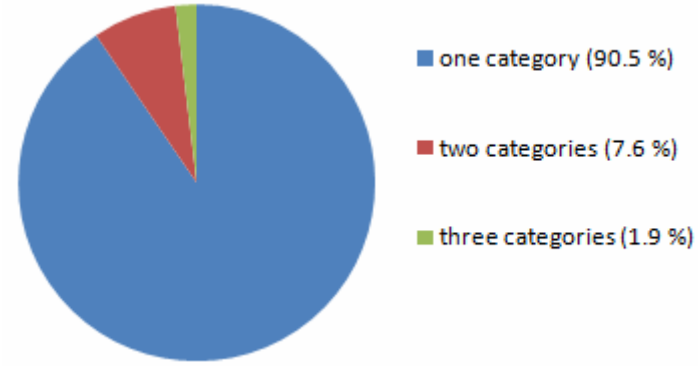


Figure 6.2: Number of categories of significant benefit per FOMP (N = 105)

Most (90.5 %; n = 95) of the 105 FOMP’s have assumptions in one of the three main categories. Only (9.5 %) of the FOMP’s have assumptions associated with two (n = 8) or three (n = 2) significant benefit categories. More detailed, 93.7 % (n = 89/95) of the FOMP’s that have assumptions associated with one category are expected to have an improved efficacy. From the 10 (9.5 %) FOMP’s that have assumptions of significant benefit related to more categories, 9 FOMP’s are at least expected to demonstrate improved efficacy. Consequently, the majority (93.3 %, n = 98 (89 + 9)) of the sponsors of FOMP’s expect to justify at least a better efficacy in comparison with the first authorized OMP for the same rare disease. It is also observed that all 16 approved FOMP’s have justified significant benefit based on the efficacy profile (e.g. “treatment for patients with resistance or intolerance to prior therapy including imatinib mesilate” (EU/3/05/339) or “an improved exercise capacity” (EU/3/03/178)).

Assumptions of significant benefit per disease class

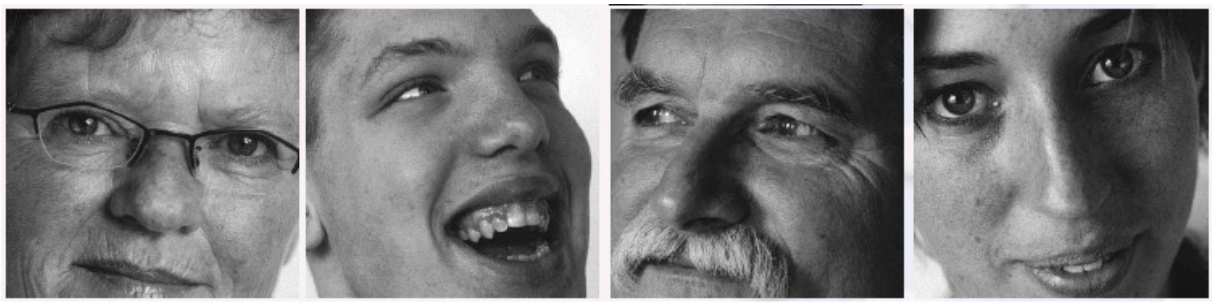
Finally, the categories of significant benefit (n = 117) of the 105 FOMP's were grouped per disease class (i.e. C00-D48 (oncology) vs. other ICD-10 classes) to explore possible similarities and/or differences between classes. The division of the three categories for the C00-D48 class vs. other ICD-10 classes is reflected in table 6.8. It is observed from table 6.8 that percentages regarding each category are comparable for the classes and moreover, that the sponsors of FOMP's in both classes are especially focusing on an improved efficacy profile.

Table 6.8: Categories of significant benefit per disease class (C00-D48 (oncology) vs. other classes)

Category of significant benefit	C00-D48 N = 85 (%)		Other classes N = 32 (%)	
Improved efficacy	73	(85.8 %)	25	(78.1 %)
Improved safety	6	(7.1 %)	3	(9.4 %)
Contribution to patient care	6	(7.1 %)	4	(12.5 %)

(copied from Stuurgroep Weesgeneesmiddelen, 2010a)

CONCLUSIONS, DISCUSSION AND POLICY IMPLICATIONS



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Chapter 7 – CONCLUSIONS, DISCUSSION AND POLICY IMPLICATIONS

Within this last chapter, the main results and conclusions of this thesis are discussed, among others, by comparing the findings with earlier research in the orphan drug field. The main conclusion of this thesis is thereafter reflected by giving an answer on the stated research question of this thesis. Subsequently, policy implications regarding this thesis are presented in the next paragraph. In the final paragraph, all performed steps of the empirical cycle of this research are discussed and furthermore, recommendations for subsequent research are presented.

Objective of this thesis

For many rare indications no safe and effective treatments have come available yet, despite the presence of orphan legislations to stimulate orphan drug development. At the same time, some rare diseases are associated with a high number of OMP's, whereas others have none. For several of the rare indications with an authorized OMP, follow-on OMP's (FOMP's) are in development or sometimes even authorized. This implies a (skewed) distribution with regard to orphan drug development and more detailed, with regard to FOMP development. As a result, part of the patients affected by a rare indication never get access to better treatments for their rare indication, despite the fact that the legislations were aimed at giving patients suffering from rare diseases access to treatments with the same quality as other patients. This thesis therefore aimed to further elucidate this (skewed) distribution. On the one hand, this thesis aimed to identify factors that explain the development of FOMP's and on the other hand, to characterize sponsors that are developing FOMP's. This resulted in the following stated main research question to be answered within this thesis: **which factors explain the development of FOMP's and how can the sponsors of FOMP's be characterized?**

7.1 Development of FOMP's

With regard to the development of FOMP's, the final multivariate model revealed one characteristic of an orphan disease as predictor for the development of at least one FOMP for rare indications with an approved OMP, namely the disease prevalence (i.e. market size). Rare diseases with an approved OMP in Europe with a prevalence above 1/100,000 have a more than 25-fold higher chance of obtaining at least one FOMP in development. In addition, an analysis of an US sample in this research confirmed that the disease prevalence (i.e. market size) is an important predictor for the development of at least one FOMP for rare indications with an authorized OMP in the USA. Our findings firstly support that the majority of the OMP's in Europe are intended for rare diseases with a prevalence above 1 per 100,000 (EMA, 2010b). Heemstra et al. (2009) furthermore concluded that the prevalence of the rare indication does matter in translation of rare disease research into the start of an orphan drug program. Besides the fact that more prevalent rare indications (> 1 per 100,000) have more first OMP's, our results confirm that, even if OMP's are in development, and finally authorized, for less prevalent rare diseases (< 1 per 100,000) this does not result in the development of FOMP's. The fact that prevalence continues to matter regarding the presence/absence of FOMP development can be explained by the fact that drug development is still risky and costly, although an authorized OMP is available. Furthermore, conducting clinical trials for rare indications is difficult as a result of practical limitations (e.g. finding enough patients). These factors, together with the small market, make a positive decision regarding the development of a follow-on OMP for a less prevalent rare indication (< 1 per 100,000) more unlikely (Heemstra et al., 2009).

In conclusion, this thesis confirms that the potential market size is a predictor for innovation in the pharmaceutical industry, as also concluded by Acemoglu and Linn (2003). Their results, however, are now also supported by data from specific the orphan drug field and emphasize the importance of the market size with regard to orphan drug development and more detailed, with regard to FOMP development.

7.2 Characterization of the sponsors of FOMP's

Business-related characteristics of the sponsors of FOMP's

From the business-related characteristics of the sponsors of FOMP's it was firstly observed that more than half of the sponsors had two or more other OD's in development and moreover, that sponsors that obtain an authorization for their FOMP had almost all previously launched an authorized OMP on the market. These findings emphasize the importance of an experienced partner in bringing an OMP to the market (Wästfelt et al., 2006) and therefore, in bringing a FOMP to the market. In addition, our findings confirm that previous experience of the sponsor is a predictor for subsequent market authorization of OMP's, as already was concluded by Heemstra et al. (2008a).

Secondly, it was observed from the descriptive statistics regarding the company's size that more than half of the FOMP's are owned by small- and medium-sized companies (SME's). The authorized FOMP's, on the other hand, are almost all launched on the market by large-sized companies. Our results confirm that mostly OD applications are submitted by SME's and moreover, that promising OMP's are subsequently licensed to or acquired by other, larger, sponsors for further development (Heemstra et al., 2008b). More detailed, according to the stated literature, around 85 % of the OD applications have been submitted by SME's (Torrent-Farnell, 2005). From the descriptive statistics presented in this thesis, however, it is concluded that around 55 % of the FOMP's originate from SME's and consequently, that 45 % of the FOMP's are owned by large-sized sponsors. According to these findings, there appears to be a tendency towards the particularly involvement in FOMP development of large-sized companies. In addition, this finding suggest that especially large-sized firms are focusing on follow-on development. Moreover, large-sized companies appear, comparable to drug development, to focus on the relative big markets in the orphan drug field, since FOMP development is mainly present for rare diseases having a prevalence above 1 per 100,000. Finally, form our results it is also observed that big pharma appear to focus on oncologic disorders. More detailed, 80.0 % of the approved FOMP's brought to the market by large-sized firms are intended for rare forms of cancer and moreover, 73.0 % of the FOMP's that are still in development by big pharma are also intended for oncologic disorders. One explanation for this focus can be that authorization of some OMP's (e.g. Glivec® and Nexavar®) for rare forms of cancer resulted in more approvals of the same OMP for other rare forms of cancer, which implies a bigger market for companies. Two other explanations can be that large-sized firms have traditionally developed products for oncologic disorders and that more firms are focusing on close substitutes of the same molecule (e.g. kinase inhibitors) (DiMasi and Paquette, 2004). In conclusion, this research observed a high involvement of the large-sized firms in FOMP development compared to OMP development. From this result it is concluded that big pharma are mainly interested in rare diseases for which FOMP development in present, namely rare diseases with a prevalence above 1/100,000 and oncologic disorders, as revealed by the multivariate models of this thesis (see table 6.2 and 6.4). The disease class was namely revealed in the US sample as a second predictor regarding the development of at least one FOMP for rare diseases with an approved OMP. To be more general, the involvement of large-sized firms in FOMP development exemplifies the growing interest of big pharma to enter the orphan drug industry, as stated by literature (e.g. GEN, 2010), with data from the orphan drug field. This growing interest

can, among others, be explained by the fact that the industry has to shift towards niche-markets, like rare diseases, due to the decreasing likelihood of success of their blockbuster strategy.

Decision of the sponsors of FOMP's to continue further development after approval of first OMP

From the analysis regarding to what extent, and for what reason, the sponsors of FOMP's decided to terminate or continue further development after market authorization of the first OMP it was observed that – except for one – all sponsors decided to continue further development. As a result, it can be concluded that sponsors of FOMP's appear to be satisfied with a shared market exclusivity with sponsors of earlier approved OMP's for the same rare indication. To be more specific, it was also observed in this thesis that if development of a FOMP was terminated, this termination mostly was related to conducting clinical trials, registration failure, lack of funding and focus on a more promising indication of the same OMP. These findings support that termination of FOMP's is not associated with the market authorization of the first OMP for the same rare indication, but that just like the majority of the pharmaceutical compounds termination resulted from safety-, efficacy- or economic-related factors, as concluded by DiMasi (2001). Our results therefore do *not* support that market authorization of the first OMP is able to create a disincentive for other pharmaceutical companies to further develop their orphan drug program for that specific rare indication, as proposed by Nachbar and Tinselboer (2008). Consequently and more general, from the findings of this thesis it is concluded that an instrument, aimed at encouraging pharma innovation for unmet medical needs, does *not* contribute to lock-in of one particularly technology (i.e. one approved OMP).

Significant benefit as reason for decision FOMP sponsors

This thesis investigated the assumptions of significant benefit to describe for what reason the sponsors of FOMP's decided to continue further development, because sponsors of FOMP's have to justify significant benefit to obtain an approval from the authorities. The descriptive statistics showed that almost all sponsors of FOMP's focus on an improved efficacy profile compared to the first approved OMP for the same rare indication. Furthermore, it can be concluded that most sponsors expect to justify an improved efficacy due to another mechanism of action, followed by the focus on another sub-group of patients of the same rare disease.

7.3 General conclusion

The stated main research question, which factors explain the development of FOMP's and how can the sponsors of FOMP's be characterized, can now be answered. Regarding factors explaining the development of FOMP's, it is concluded that the market size (i.e. disease prevalence) is an important predictor for the development of at least one FOMP for rare diseases with an approved OMP. Moreover, in the US sample, the disease class (i.e. oncology) was found as second predictor for the development of at least one FOMP for rare diseases with an approved OMP. FOMP sponsors, and even more the sponsors of authorized FOMP's, are characterized by a high percentage of experienced and large-sized sponsors. Moreover, further characterization of FOMP development reveals a strong preference by large-sized sponsors for orphan drug development for rare diseases having a prevalence above 1 per 100,000 and oncologic disorders. Finally, the sponsors appear to be satisfied with a shared market exclusivity due to their positive decision regarding further development after market approval of the first OMP for the same rare indication. As a result, the market exclusivity instrument does *not* create a disincentive for other sponsor to invest in rare indications with an authorized OMP. In addition, almost all sponsors expect to justify significant benefit by showing an improved efficacy profile compared to the first approved OMP.

7.4 Policy implications

This paragraph elaborates policy implications with regard to the skewed distribution of OMP's and with regard to sub-question 6, i.e. which policy implications regarding stimulating pharma innovation (for unmet medical needs) by means of regulation can be derived from the results of this thesis in general?

Addressing the skewed distribution

The aim of this research was to further elucidate the observed (skewed) distribution of OMP's, and more detailed of FOMP's. It is concluded that there is a skewed distribution for the translation of rare disease research into the start of an orphan drug development program, for authorized OMP's and even for FOMP development. It appears that especially patients affected by a rare indication with a prevalence above 1/100,00 have a higher chance to get access to better treatments, because FOMP development is mainly present for these rare indications. The current legislation is thus not sufficient to give all patients suffering from orphan diseases access to treatments with the same quality as other patients.

To address the skewed distribution, additional (financial) incentives have to be implemented to encourage drug development for rare indications with a prevalence below 1/100,000, as already recommended by Heemstra et al. (2009). Possible suggestions regarding these incentives can be related to an extended market exclusivity period for these diseases, adaptation of the prevalence criteria of 5/10,000 or further stimulation of research to non-oncologic disorders. Moreover, the large-sized sponsors involved in FOMP development have often obtained the necessary experience to bring a FOMP to the market, however, also the FOMP's owned by SME's (i.e. 55 %) should be able to obtain market authorization in order to provide better treatments for patients with rare diseases. To address the skewed distribution it is thus also important to focus on SME's. The EMA addresses this issue by giving sponsors the possibility of protocol assistance and scientific advice. Moreover, the EMA launched a SME office dedicated to (regulatory) needs of SME's (EMA, 2010d). This thesis recommends, on the other hand, that SME's acquire the necessary experience within their firm, for example, by bringing an experienced management on board (based on Heemstra et al., 2008a) or by seeking collaboration with more larger, experienced, firms (e.g. the collaboration of Bayer and Onyx already started in 1994 and resulted in the authorization of Nexavar® in 2006 (Onyx, 2010b)).

In conclusion, to address the skewed distribution, this thesis recommends, on the one hand, to focus on additional (financial) incentives for rare indications with a prevalence below 1 per 100,000 and on the other hand, to support inexperienced sponsors (mostly SME's) in bringing a product to the market.

Stimulating pharma innovation (for unmet medical needs) (i.e. sub-question 6)

To stimulate the willingness of the pharmaceutical industry to invest in markets having unmet medical needs, and thereby addressing the innovation deficit, several policy measures have been implemented. This thesis focused on two important policy measures, i.e. the European Orphan Drug Regulation (EODR) and Orphan Drug Act (ODA). Based on the results of this thesis, it appears that (big) pharma have a growing interest to invest in niche-markets, like orphan diseases. Furthermore, incentives, such as a market exclusivity period, do not create disincentives for other pharmaceutical companies to invest in these markets having unmet medical needs. It can thus be concluded that regulations (i.e. policy measures) are helpful to stimulate pharma innovation (for unmet medical needs) and to address thus the innovation deficit of the industry. However, possible new policy measures aimed at stimulating pharma innovations (for unmet medical needs) have to take into account two issues based on the findings of this thesis. First, their incentives have to focus on addressing all the unmet medical needs equally, because this thesis

confirmed a skewed distribution. Second, they also have to pay attention to more inexperienced sponsors (mostly SME's) to give these companies the possibility to bring a product to the market and thus to fully benefit from the provided incentives of the regulation.

7.5 Discussion of this thesis

This paragraph discusses all the steps of the empirical cycle of this thesis. Moreover, recommendations for further research are given in this last paragraph.

This thesis started with the objective of elucidating the observed (skewed) distribution with regard to orphan drug development by focusing on FOMP development to extend the research of Heemstra et al. (2009). This could be a possible limitation and as a result, further studies could be aimed at focusing on all phases regarding orphan drug development. However, by including, among others, the same variables as Heemstra et al. (2009), the findings of this thesis could be compared with their study. More detailed, our results indeed confirm the skewed distribution of Heemstra et al. (2009) and the EMA and FDA. Consequently, combining the results of both studies give a good overview of the skewed distribution over all phases of orphan drug development.

The European Orphan Drug Regulation (Europe) and Orphan Drug Act (USA) have much in common, although differences regarding the incentives and criteria exist. As a result, this thesis was mainly delineated to Europe, instead of including Europe and the USA. Besides Europe, however, also the USA is a big and important market in the orphan drug field. Not including this important market was thus a limitation of this thesis. Consequently, to deal with this limitation, some analyses were conducted for the USA in this thesis to confirm the main findings of the European sample. First, an US sample was analyzed for factors that explain the development of FOMP's. As earlier mentioned, comparable to the EU sample, a significant association was found for the disease prevalence. In addition, an association was found for disease class in the US sample, while in the EU sample no association was observed for this variable. This is, among others, explained by the distribution of the included rare diseases in the US sample over the ICD-10 classes. In the US sample a relatively high percentage of rare diseases belonged to the ICD-10 class A00-B99 (infectious and parasitic diseases), while in the EU sample no disease was included in this class. Moreover, the US sample included more cases than the EU sample (71 vs. 44), resulting in more statistically power of the US sample. Second, for the characterization of sponsors of FOMP's, only the decision of sponsors in the USA was examined to confirm the (unexpected) outcome of the EU sample. In conclusion, although this thesis investigated some important results for an US sample, it is recommended for further studies to extend the analyses of the US sample. Especially, the business-related characteristics of sponsors of FOMP's have to be investigated to get insight in to what extent sponsors in the USA are comparable to Europe, since European sponsors appear to have specific (i.e. large-sized and experienced) characteristics. In addition, all dimensions of the market-, product- and disease-related characteristics of the conceptual model have to be examined for the US sample, because this thesis only included the five dimensions for which statistically significant relations were found in the univariate analyses of the EU sample. Examining both the USA and Europe, makes it possible to generalize the findings and conclusions of this thesis to FOMP development in general (i.e. on an international level). As a result, the external validity (i.e. generalizability) of the findings of this thesis will increase.

The scientific relevance of this research was related to the fact that the industry has to shift towards niche-markets (e.g. orphan diseases), due to the decreasing likelihood of success of their blockbuster strategy. Our findings with

regard to the involvement of a high percentage of large-sized firms indicate the growing interest of big pharma to enter niche-markets with data from one of these niche-markets, i.e. the orphan drug field. As a result, findings of this thesis can be useful to strengthen the debate regarding the shift of big pharma towards niche-markets. On the other hand, the social relevance was related to giving all patients affected by a rare indication access to better, and finally optimal, treatments. Our findings showed two important issues, i.e. equally addressing the unmet medical needs and focusing on inexperienced sponsors, to focus on in order to address this skewed distribution and thereby giving patients suffering from an orphan disease access to better treatments.

This thesis tested a model, based on prerequisites that comply to successful pharma innovations, to identify factors explaining the development of at least one FOMP for rare diseases with an approved OMP. The model enclosed a wide range of variables that were expected to influence FOMP development, based on earlier research. The choice of the variables included in the model of this research was demarcated by the used framework of Van Noordwijk (1984). This framework has as advantage that it includes a wide range of factors involved in drug development. A disadvantage, however, is that the three requirements complying to a successful pharmaceutical innovation can be interpreted in different ways (Buurma et al., 2005). As a consequence, it can be that different researchers include different dimensions regarding each prerequisite. To deal with this limitation, this thesis tried to include aspects of recent studies in the orphan drug field, however, the explained variance of the final model was just 38.8 %. This percentage of 38.8 % implies the existing of some unforeseen, yet unspecified, factors regarding the development of FOMP's for rare diseases with an approved OMP. On the other hand, 81.8 % of the dependents variable's value is predicted correctly by the used conceptual model. Moreover, this thesis only observed a causal relationship for the market-related characteristics, and not for the product-related and disease-related characteristics. A theoretical implication is therefore that the framework of Van Noordwijk (1984), related to a successful pharma innovation, not encloses all the explanatory factors for FOMP development and therefore provided not a complete preliminary answer the question 'which factors explain the development of FOMP's?' However, no complete model regarding FOMP development exists yet. Further research has thus, on the one hand, to include additional dimensions for the requirements (e.g. heterogeneity patient population for disease-related characteristics) and on the other hand, characteristics that were not included in the conceptual model (e.g. social-related characteristics (based on Milne, 2002)). Consequently, the conceptual model will give a better preliminary answer on block one of the stated main research question and as a result, the internal validity of the findings of this thesis will increase.

A strong point of this thesis was the construct validity. Variables of the conceptual model were operationalized by international classifications (i.e. ICD-10 of the WHO) or by measurements of earlier research. This contributed to the establishment of correct operational measurements for the variables. Furthermore, data was only collected in the public domain regarding all variables. As a result, other researchers are expected to collect the same data as in this thesis, and thus get the same findings as in this thesis. Consequently, the findings of this thesis have a good reliability.

This thesis has used the same method of analysis as Heemstra et al. (2008a and 2009) to analyze block one of the conceptual model, which made it possible to compare the findings with, among others, their research. Concerning the data analyses of block two (characterization of sponsors of FOMP's) of our model, however, some discussion points have to be reflected. For the business-related characteristics only descriptive statistics have been performed (instead of statistical analyses). It is thus harder to draw conclusions from the results. However, the results showed

a strong indication for the involvement of large and experienced firms in FOMP development and it is therefore expected that statistical analyses confirm our findings. The outcome for the decision of the sponsors of FOMP's to continue or terminate further development is based on data in the public domain. More detailed, the outcome was based on choices made by the researcher after evaluating the available data. Furthermore, also the assumptions of significant benefit were categorized after data collection by the researcher using the EMA guideline. It is therefore possible that other researchers interpret data regarding the decision and the assumptions of significant benefit in another way, and thus get other results. To deal with this limitation all analyses are made by one researcher and in addition, all performed steps are written down in a detailed way to increase the reliability. Our findings, however, show strong indications for the positive decision of sponsors based on an expected better efficacy and as a result, it is expected that other sponsors are able to get the same findings.

Despite the above mentioned limitations, which have to be taken into account, the results and thus conclusion of this thesis still remain intact, because this research observed strong indications for all the investigated aspects. As a consequence, the findings of this thesis give a satisfactory answer to the research question 'which factors explain the development of FOMP's and how can the sponsors of FOMP's be characterized?' However, regarding further research, the largest advantage can be obtained from including additional factors that explain the development of FOMP's. As a result, the internal validity of the results will increase. In addition, further studies have to include samples of Europe and the USA for all the investigated aspects of the research question to be able to compare both markets. As a result, the generalizability (i.e. external validity) of all findings of this thesis will then increase.

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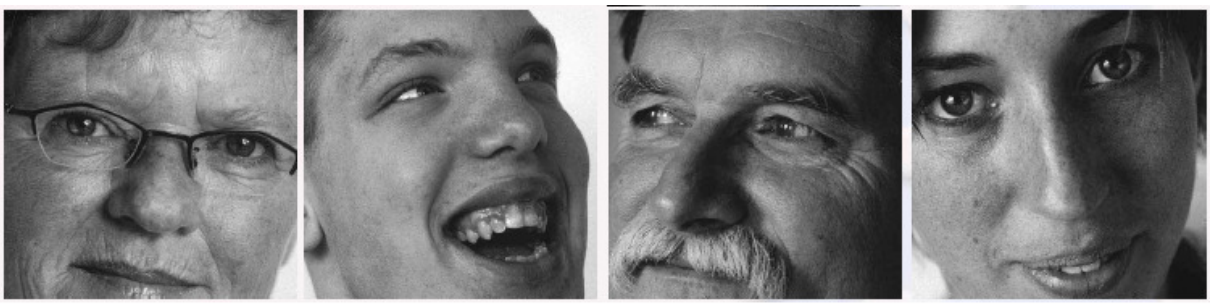

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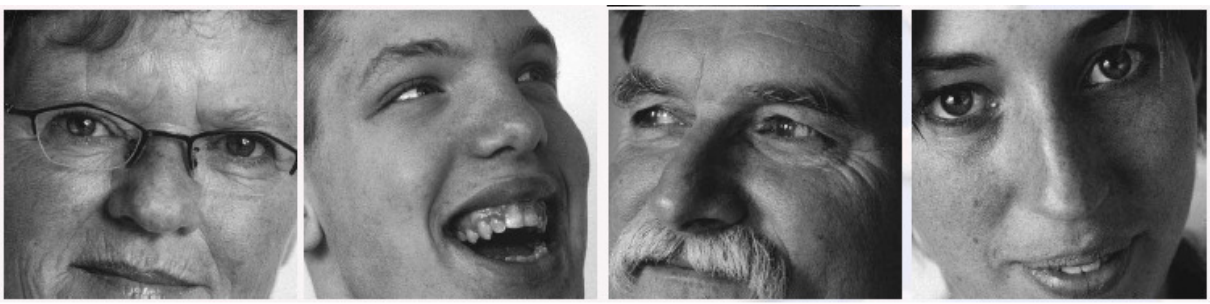
APPENDICES



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APPENDIX I – HISTORY, FACTS AND FIGURES ODA (USA) AND EODR (EUROPE)

The USA was in 1983 the first country in the world implementing a legislation aimed at stimulating orphan drug development, i.e. the Orphan Drug Act (ODA) (Cheung et al., 2004). The ODA has had a substantial impact on public health and represents nowadays one of the most successful policy measures of the recent history within the USA (Haffner et al., 2002). The successes of the ODA contributed to the implementation of legislations in other countries. Following the USA (1983), Singapore (1991), Japan (1993) and Australia (1998), in April 2000 Europe finally introduced the European Orphan Drug Regulation (EODR) having the objective to stimulate the research and development of orphan drugs. Besides these legislations, also national incentives in the Netherlands regarding rare indications are implemented (Heemstra, 2010). This appendix firstly provides an overview of both the ODA and EODR as well as the national incentives in the Netherlands. To conclude, some facts and figures with regard to orphan drug development in the USA and Europe are presented.

I.1 Orphan Drug Act (USA)

During the late 1950s and the early 1960s, the pharmaceutical world was characterized by the thalidomide scandal (Wellman-Labadie and Zhou, 2010; Cheung et al., 2004; Haffner et al., 2002). Thalidomide was authorized as a medicine against morning sickness in pregnant women, however, taking the drug during the first trimester of the pregnancy resulted in tragic birth defects (FDAReview.org, 2010; Cheung et al., 2004; Haffner et al., 2002). As a result of this thalidomide scandal, the Kefauver-Harris Bill amendments were added in 1963 to the US federal Food, Drug and Cosmetic Act of 1938 (FD&C Act) (FDAReview.org, 2010). These amendments mandated that all medicinal products have to be demonstrated to be safe and effective by doing adequate and controlled clinical trials before obtaining market approval from the authority (i.e. the FDA) (Haffner et al., 2002). On the one hand, the public protection from possible unsafe medicines improved, on the other hand, the costs of drug development enormously increased for the pharmaceutical industry. Consequently, the industry decided to focus on indications with a large population to have the possibility to earn back their investments. At the same time, rare diseases were ignored by the industry and became ‘orphaned’ (Wellman-Labadie and Zhou, 2010; Cheung et al., 2004; Haffner et al., 2002). As a result, the Kefauver-Harris Bill amendments contributed to an increasing gap in the availability of treatments for common and rare diseases.

The situation of patients suffering from an orphan disease became a public issue in the USA due to lobbying of patient and non-governmental organizations (e.g. the National Organization of Rare Diseases (NORD)) during the late 1970s and the early 1980s (Cheung et al., 2004). On January 4, 1983, President Ronald Reagan of the USA signed the Orphan Drug Act (ODA), which had the objective to stimulate the research and development of rare diseases (Wellman-Labadie and Zhou, 2010; Cheung, 2004; Haffner et al., 2002). By the amendment of 1984, an orphan disease was defined as (1) an indication affecting less than 200,000 persons in the United States or (2) an indication affecting more than 200,000 persons in the United States, however, there is no expectation that research and development costs are earned back by revenues of the orphan drug (FDA, 2010b). The threshold of 200,000 persons in the USA was an arbitrary choice based on the estimated prevalence of the indications multiple sclerosis and narcolepsy (Department of Health and Human Services, 2001). Furthermore, the amendment of 1988 required sponsors to obtain an orphan designation (OD) prior before submitting for a market authorization by the FDA (Department of Health and Human Services, 2001).

To obtain such an OD for a medicinal product, sponsors have to send an application form to the Office of Orphan Product Development (OOPD) of the FDA. In this application form sponsors have to establish that their medicinal product is intended for an indication affecting less than 200,000 patients in the USA and moreover, they have to illustrate (with data) that their OMP seems to be 'promising' (Coté, 2010). The OOPD has to react within 60 days, however, the process lasts longer if the office needs additional information from sponsors (Department of Health and Human Services, 2001). Sponsors having required an OD from the OOPD for their medicinal products are entitled to incentives like tax credits of (maximum) 50 % of clinical trial costs, protocol assistance, waiver of drug application fees and grants for orphan drug development (Wellman-Labadie and Zhou, 2010; Griggs et al., 2009; Haffner et al., 2002). More detailed, this grant program, having an annual budget of 14 million US dollar, aims to assists sponsors in discharging the costs of their clinical trials (Griggs et al., 2009).

The most important incentive encouraging orphan drug development is a seven years market exclusivity period upon the approval (Cheung et al., 2004; Haffner et al., 2002). During these seven years of exclusivity, no similar competitive product can obtain market approval from the FDA unless clinical superiority is demonstrated (Dear et al., 2006; Meyers and Lipucci Di Paola, 2003; Department of Health and Human Services, 2001). Clinical superiority is justified as the OMP: (1) is more effective compared to an approved OMP (assessed by a clinically meaningful endpoint in adequate clinical trials); (2) is more safe compared to an approved OMP (in a substantial part of the target population) or (3) makes otherwise a major contribution to patient care, in the absence of a better efficacy or safety, than an approved OMP (Orphan Drug Regulations, 21 CFR 316.3, 2005; Department of Health and Human Services, 2001; Bollylky, 2009).

I.2 European Orphan Drug Regulation (Europe)

Before April 2000, none of the member states of the European Union had a well defined orphan drug legislation (Cheung et al., 2004). Only a few countries, like the United Kingdom, France and Sweden, had some incentives encouraging the research and development of orphan drugs (Cheung et al., 2004). In general, however, both on national and European level limited action had been taken to stimulate research and development of orphan drugs. The European Commission (EC) therefore recognized that such action had preferably to be taken on Community level to have advantage of market size and to avoid dispersal of limited resources (Commission of the European Communities, 2000).

Orphan diseases were identified in 1993 in Europe as a priority area within the field of public health as a result of lobbying and advocacy making by particularly the (French) patient organizations and the European federation of patient associations between member states (the European Organization for Rare Disorders (Eurordis)) (Meyers and Lipucci Di Paola, 2003; Commission of the European Communities, 2000). On December 16, 1999, the European Parliament adopted regulation (EC) No 141/2000, which became effective in April 2000 (Commission of the European Communities, 2000). The objective of this legislation was stimulating drug development for rare diseases by providing incentives to the pharmaceutical industry (EMA, 2009). Thereby, it gives patients affected by rare indications access to treatments with the same quality as other patients (EMA, 2009; Dear et al., 2006). Although the EODR is mainly based on the ODA, the establishment of the EODR was preceded by a comparative analysis of all available orphan legislations by the Scientific Technology Options Assessment (STOA) Unit of the European Parliament (Rinaldi, 2005).

In the European Medicines Agency (EMA) the Committee for Orphan Medicinal Products (COMP) was formed, being responsible for all European OD applications (Commission of the European Communities, 2000). To obtain an OD for a medicinal product a sponsor has to submit an application form to the COMP, which is possible at any stage during development (Commission of the European Communities, 2000). Sponsors have to demonstrate in their application that their medicinal product: (1) is intended for a rare indication with a maximum prevalence of 5 patients per 10,000 inhabitants; (2) is intended for a life threatening or seriously debilitating indication and most important (3) is of significant benefit compared to the existing treatments (including authorized OMP's) at time of designation. The COMP forms an opinion with regard to the OD application within 90 days. This opinion will be forwarded to the EC, which shall adopt the decision within 30 days. All the OD's are reported in the Community Register of Orphan Medicinal Products of the EMA (Commission of the European Communities, 2000). While the COMP reviews the OD applications, the Committee for Medicinal Products for Human Use (CHMP) forms an opinion about the market approval of an OMP by reviewing its quality, safety and efficacy. The opinion of the CHMP is also forwarded to the EC, which makes the final decision for market approval (Voordouw, 2009).

OMP's are entitled to the following incentives within Europe: protocol assistance (scientific advice regarding the necessary trials to show quality, safety and efficacy); fee waivers; funded research (grants for research from the member states and community) and access to the centralized procedure of the EMA, which is the most simplest and quickest way of launching a treatment on the European market (Wästfelt et al., 2006; Meyers and Lipucci Di Paola, 2003). However, the main incentive encouraging orphan drug development is a ten years period of market exclusivity upon authorization. During this period the community and member states shall not approve another OMP for the same rare disease (Commission of the European Communities, 2000). Nevertheless, more than one approved OMP for the same disease is allowed by the European legislation if: (1) the sponsor of the first approved OMP gives consent that the OMP could be authorized; (2) the sponsor of the first authorized OMP is not able to supply sufficient quantities of the product or (3) the sponsor shows that the OMP, although similar, is safer, more effective or otherwise clinically superior to the first authorized OMP (Commission of the European Communities, 2000).

I.3 National incentives in the Netherlands

Already in 1998, the Dutch Raad voor Gezondheidsonderzoek (RGO) provided advice on how to improve aspects of research on rare indications and orphan drugs in the Netherlands (Heemstra, 2010). The RGO concluded that it would be wishful to collect and coordinate initiatives. More detailed, "the RGO advised to create an independent steering committee in which all parties involved would participate" (Heemstra, 2010: 12). At 12 April 2001, the Steering Committee on Orphan Drugs (in Dutch: Stuurgroep Weesgeneesmiddelen (WGM)) was appointed by the former minister of health Els Borst. In the steering committee representatives of different stakeholders, like the industry, scientists, pharmacists and patient organizations, of the Dutch orphan drug field are participating. In general, the committee aims to stimulate orphan drug development and to improve the situation of patients with a rare disease, mainly to reinforce information transfer on rare diseases (Stuurgroep Weesgeneesmiddelen, 2010b).

I.4 Facts and figures

In 2006, between 5,000 and 8,000 different rare diseases are known worldwide. More detailed, in January 2008 the National Organization of Rare Diseases (NORD) listed 6,819 different rare indications in the USA (Seoane-

Vazquez et al., 2008; Wästfelt et al., 2006). Moreover, every year an estimated 250 new ones are discovered as a result of our improving knowledge on genomics and disease biology (Heemstra et al., 2008a; Wästfelt et al., 2006; Haffner et al., 2002). Furthermore, approximately 20 to 25 million people in the USA and about 30 million people in Europe are affected by one of these diseases, which is comparable to 8-12 % and 6-8 % of the population in the USA and Europe respectively (Griggs et al., 2009; Seoane-Vazquez et al., 2008; Wästfelt et al., 2006).

With a total of more than 2,180 OD's and 349 authorized OMP's between 1983 and June 2010 the ODA is highly successful (based on data from the FDA, 2010a). Moreover, Cheung et al. (2004) argued that without incentives of the ODA a significant percentage of the population in the USA would not have access to adequate treatments for their rare indications yet. Because, during the 1970s and the early 1980s less than 10 authorized OMP's were available on the market (Department of Health and Human Services, 2001; Rinaldi, 2005). On the other hand, in Europe more than 725 medicinal products obtained an OD and 58 OMP's are authorized since the introduction of the EODR up to June 2010 (based on data from Orpha.net, 2010a; European Commission, 2010a). These numbers show that the EODR is also starting to play an important role in orphan drug development (Heemstra, 2010).

Figure I.1 presents the approved OMP's in both the USA and Europe between 2001 and 2008 (i.e. study period of this thesis) (based on data from FDA, 2010a; Orpha.net, 2009a; European Commission, 2010a). As depicted in the figure, in the USA more OMP's obtained approval than in Europe from 2001-2008. Dear et al. (2006) argued that this difference can be explained by one of the incentives provided by the ODA, namely tax credits. In Europe tax credits are not feasible as incentive, because taxation is individually controlled by all member states. Despite this discrepancy, it is concluded that both the ODA of the USA and the EODR of Europe are successful in stimulating the research and development of orphan drugs and the availability of adequate treatments for patients affected by a rare disease (Cheung et al., 2004). However, more than 7,000 rare diseases are known and therefore more efforts are still necessary. Nevertheless, more than 2.6 million patients in Europe and an estimated 11 million patients in the USA suffering from a rare indication benefit from one of the authorized OMP's yet (EMA, 2010b; Haffner et al., 2002).

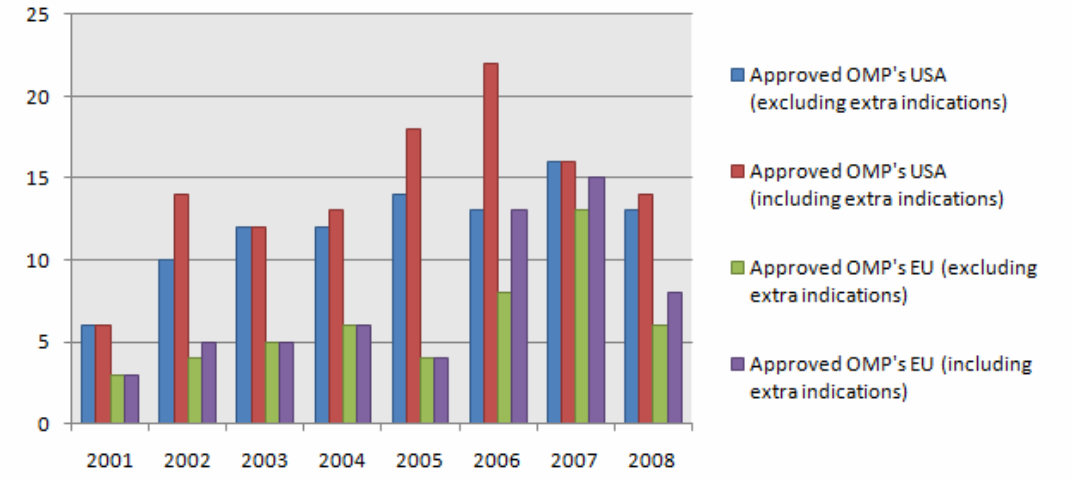

Figure I.1: Authorized OMP's in the period 2001 – 2008 in Europe and the USA
(based on data from European Commission, 2010a; Orpha.net, 2009a; FDA, 2010a)

(*) Including extra indications, means that an OMP approved for more rare diseases (e.g. Glivec® for chronic myeloid leukemia and gastrointestinal stromal tumor) is counted more times. While, excluding rare indications, means that an OMP approved for more rare diseases (e.g. Glivec®) is only counted one time (i.e. in the year the first market approval was obtained).

APPENDIX II – EXTENDED OVERVIEW OF THE EU SAMPLE: RARE INDICATIONS AND THEIR RELATED APPROVED OMP

Table II.1: Extended overview of the European sample: rare indications and their related approved OMP (based on data from Orpha.net, 2009a and European Commission, 2010a)

#	Rare indication	#	Authorized OMP('s)	Year	E = experimental C = control
1	Treatment of Fabry disease	1	Replagal	2001	E 01/26
		2	Fabrazyme	2001	
2	Treatment of chronic myeloid leukemia	3	Glivec I	2001	E 02/26
		4	Sprycel I	2006	
		5	Tasigna	2007	
3	Treatment of Gaucher disease	6	Zavesca	2002	E 03/26
4	Treatment of acute promyelocytic leukemia	7	Trisenox	2002	E 04/26
5	Treatment of pulmonary arterial hypertension	8	Tracleer I	2002	E 05/26
		9	Ventavis	2003	
		10	Revatio	2005	
		11	Thelin	2006	
		12	Volibris	2008	
6	Treatment of acromegaly	13	Somavert	2002	E 06/26
7	Treatment of gastrointestinal stromal tumors	14	Glivec II	2002	E 07/26
8	Treatment of familial adenomatous polypopsis	15	Onsenal	2003	E 08/26
9	Treatment of NAGS-deficiency	16	Carbaglu	2003	C 01/18
10	Treatment prior to hematopoietic progenitor cell transplantation	17	Busilvex	2003	C 02/18
11	Treatment of mucopolysaccharidosis type I	18	Aldurazyme	2003	C 03/18
12	Treatment of essential thrombocythaemia	19	Xagrid	2004	C 04/18
13	Treatment of Wilson's disease	20	Wilzin	2004	E 09/26
14	Treatment of high-grade dysplasia in Barrett's oesophagus	21	Photobarr	2004	C 05/18
15	Treatment of patent ductus arteriosus	22	Pedea	2005	C 06/18
16	Treatment of adrenal cortical carcinoma	23	Lysodren	2004	E 10/26
17	Treatment of hairy cell leukemia	24	Litak	2004	E 11/26
18	Treatment of narcolepsy	25	Xyrem	2005	E 12/26
19	Treatment of chronic pain requiring intraspinal analgesia	26	Prialt	2005	C 07/18
20	Treatment of tyrosinaemia type I (hereditary)	27	Orfadin	2005	C 08/18
21	Treatment of dermatofibrosarcoma protuberans	28	Glivec III	2006	C 09/18
22	Treatment of acute lymphoblastic leukemia	29	Evoltra	2006	E 13/26
		30	Glivec IV	2006	
		31	Sprycel II	2006	
		32	Atriance	2007	
23	Treatment of anthracycline extravasations	33	Savene	2006	C 10/18
24	Treatment of renal cell carcinoma	34	Nexavar I	2006	E 14/26
		35	Torisel	2007	
25	Treatment of mucopolysaccharidosis type VI	36	Naglazyme	2006	C 11/18
26	Treatment of glycogen storage disease type 2 (Pompe disease)	37	Myozyme	2006	E 15/26

Continuation table II.1: Extended overview of the European sample: rare indications and their related approved OMP (based on data from Orpha.net, 2009a and European Commission, 2010a)

#	Rare indication	#	Authorized OMP('s)	Year	E = experimental C = control
27	Treatment of chronic iron overload requiring chelation therapy	38	Exjade	2006	E 16/26
28	Treatment of hypereosinophilic syndrome	39	Glivec V	2006	E 17/26
29	Treatment of myelodysplastic syndromes	40	Glivec VI	2006	E 18/26
		41	Vidaza I	2008	
30	Treatment of hepatocellular carcinoma	42	Nexavar II	2007	E 19/26
31	Treatment of soft tissue sarcoma	43	Yondelis	2007	E 20/26
32	Treatment of paroxysmal nocturnal haemoglobinuria	44	Soliris	2007	C 12/18
33	Treatment of sickle cell syndrome	45	Siklos	2007	E 21/26
34	Treatment of multiple myeloma	46	Revlimid	2007	E 22/26
		47	Thalidomide	2008	
35	Treatment of Lennox-Gastaut syndrome	48	Inovelon	2007	C 13/18
36	Treatment of severe primary IGF-1 deficiency	49	Increlex	2007	C 14/18
37	Treatment of mucopolysaccharidosis type II (Hunter syndrome)	50	Elaprase	2007	C 15/18
38	Treatment of severe myoclonic epilepsy in infancy (Dravet's syndrome)	51	Diacomit	2007	C 16/18
39	Treatment of homocystinuria	52	Cystadane	2007	C 17/18
40	Treatment of systemic sclerosis	53	Tracleer II	2007	E 23/26
41	Treatment of chronic myelomonocytic leukemia	54	Vidaza II	2008	C 18/18
42	Treatment of hyperphenylalaninaemia (phenylketonuria)	55	Kuvan	2008	E 24/26
43	Treatment of angioedema (hereditary)	56	Firazyr	2008	E 25/26
44	Treatment of acute myeloid leukemia	57	Ceplene	2008	E 26/26
		58	Vidaza III	2008	

APPENDIX III – VALIDITY MULTIVARIATE MODEL DEVELOPMENT OF FOMP'S (EU SAMPLE)

Table III.1 demonstrates that the pseudo R^2 value of the final multivariate model (see step 5) of the tested model is 38,8 %. Furthermore, from table III.2 it is observed that the overall percentage of correctly predicted values of the dependent variable (see step 5) is 81.8 %.

Table III.1: Pseudo R^2 value of the final multivariate model (Europe)

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	27,493[a]	,356	,494
2	27,776[a]	,350	,487
3	28,072[a]	,344	,478
4	29,377[a]	,318	,442
5	31,198[b]	,279	,388

Table III.2: Overall percentage of correctly predicted values of the dependent variable (Europe)

			Predicted Dependent		
	Observed		,00	1,00	Percentage Correct
Step 1	Dependent	,00	7	4	63,6
		1,00	1	21	95,5
		Overall Percentage			84,8
Step 2	Dependent	,00	7	4	63,6
		1,00	1	21	95,5
		Overall Percentage			84,8
Step 3	Dependent	,00	6	5	54,5
		1,00	1	21	95,5
		Overall Percentage			81,8
Step 4	Dependent	,00	6	5	54,5
		1,00	1	21	95,5
		Overall Percentage			81,8
Step 5	Dependent	,00	6	5	54,5
		1,00	1	21	95,5
		Overall Percentage			81,8

APPENDIX IV – DEVELOPMENT OF FOMP'S IN THE USA

➢ Sample

Comparable to Europe, authorized OMP's intended for either the diagnosis or prevention of a rare indication are excluded from the sample. Moreover, authorized OMP's for rare diseases belonging to the ICD-10 class S00-T98 (injury, poisoning and certain other consequences of external causes) are excluded from the US sample. Because, the COMP in Europe did not recognize such indications as rare diseases (e.g. the treatment of known or suspected cyanide poisoning).

A total of 85 OMP's intended for the treatment of an orphan disease obtained market authorization from the FDA in the period 1 January 2001 – 31 December 2008 (based on data from FDA, 2010a). Comparable to the European sample, most of these authorized OMP's are intended for the treatment of one rare indication. However, products like Gleevec®, Revlimid® and Alinia® are launched on the market for more than one rare indication, resulting in a total of 98 authorized orphan indications in the USA. Together these 98 authorized indications are launched on the market for the treatment of 71 different rare indications. The experimental group of the US sample included 38 of the 71 rare indications, which means that 53.5 % of the rare indications in the USA have at least one FOMP. As a result, 33 of the 71 (46.5 %) rare indications had no FOMP and were included in the control group.

In line with the European sample, the experimental and control group were compared on different characteristics. However, only the statistically significant characteristics of the univariate analyses of the European sample were included in this US analysis (the age of onset, disease prevalence, disease-specific scientific output, disease class and finally, the turnover of the first authorized OMP), because of practical limitations (i.e. time). All the results of the descriptive statistics, univariate analyses and multivariate analysis are presented hereafter.

➢ Descriptive statistics (see table IV.1 on the next page)

Approximately one quarter (23.9 %) of the rare indications belong to the class of oncologic disorders (i.e. C00-D48). Regarding the disease-specific scientific output it is observed that around two third (67.6 %) of the included orphan diseases have more than 655 scientific publications in PubMed. Furthermore, the majority (81.0%) of the rare diseases in the sample have a prevalence of more than 1 patient per 100,000 inhabitants. More detailed, only 5.6 % of the rare diseases included in the experimental group has a prevalence of < 1/100,000, while in the control group 37.0 % of the rare indications has a prevalence below 1 patient per 100,000 inhabitants. Regarding the age of onset, it is observed that 41.4 % of the rare diseases have an age of onset in childhood. To conclude, more than half (53.7 %) of the first authorized OMP's have an annual turnover of more than 175 million US dollar.

➢ Univariate analyses

For three included variables statistically significant associations were observed, namely the disease class, disease prevalence and disease-specific scientific output. The observed relations were strongest for both the disease class and the disease prevalence. More specific, the results show that oncologic disorders with a first authorized OMP have a 10-fold increased likelihood to obtain at least one FOMP compared to rare diseases in other ICD-10 classes (OR = 10.1; CI = 2.1-48.6). In addition, also rare indications with an authorized OMP and a prevalence above 1 per 100,000 inhabitants have a 10-fold increased chance on FOMP's than rare indications with less than 1 patient per 100,000 inhabitants (OR = 10.0; CI = 2.0-50.8). Finally, the results revealed a statistically significant relation

for the disease-specific scientific output. Rare diseases with more than 655 scientific publications in PubMed have a more than 4-fold increase in the chance to obtain at least one FOMP than rare indications having less than 655 scientific publications in PubMed (OR = 4.2; CI = 1.4-12.1).

Table IV.1: Results univariate analyses (USA)

Dimension	Indicator	Total (N = 71) (%)		Experimental group (N = 38) (%)		Control group (N = 33) (%)		OR (95 % CI)
Class	other class	54	(76.1 %)	23	(60.5 %)	31	(93.9 %)	reference level
	C00-D48	17	(23.9 %)	15	(39.5 %)	2	(6.1 %)	10.1 (2.1 – 48.6)
Prevalence 2 categories(*)	< 1/100,000	12	(19.0 %)	2	(5.6 %)	10	(37.0 %)	reference level
	> 1/100,000	51	(81.0 %)	34	(94.4 %)	17	(63.0 %)	10.0 (2.0 – 50.8)
Scientific output	< 655 publications	23	(32.4 %)	7	(18.4 %)	16	(48.5 %)	reference level
	> 655 publications	48	(67.6 %)	31	(81.6 %)	17	(51.5 %)	4.2 (1.4 – 12.1)
Childhood(*)	adulthood	34	(58.6 %)	21	(65.6 %)	13	(50.0 %)	reference level
	childhood	24	(41.4 %)	11	(34.4 %)	13	(50.0 %)	0.5 (0.2 – 1.5)
Turnover first authorized OMP(*)	< 175 million US $	25	(46.3 %)	14	(43.8 %)	11	(50.0 %)	reference level
	> 175 million US $	29	(53.7 %)	18	(56.2 %)	11	(50.0 %)	1.3 (0.4 – 3.8)

(*) Percentage prevalence is based on N = 63, 36 and 27 respectively
(*) Percentage childhood is based on N = 58, 32 and 26 respectively
(*) Percentage turnover first authorized OMP is based on N = 54, 32 and 22 respectively

➢ Multivariate analysis

As a second step, a multivariate analysis was performed, including the three variables with statistically significant associations (p value < 0.05). Table IV.2 depicts the results of this multivariate analysis. The final model showed two characteristics as predictor for the chance to obtain at least one FOMP as rare disease with an approved OMP, namely the disease prevalence and the disease class (OR = 6.3; CI = 1.2-33.4 and OR = 5.9; CI = 1.2-30.0). The pseudo R^2 value of this model is 0.305, which implies that 30.5 % of the dependent's variance has been explained (see table IV.3, step 2). Moreover, the overall percentage of correctly predicted values of the dependent variable is 69.8 %, as depicted in table IV.4 on the next page (see step 2).

Table IV.2: Results multivariate analysis (USA)

Dimension	Indicator	OR[1] (95 % CI)
Prevalence	< 1/100,000	reference level
	> 1/100,000	6.3 (1.2 – 33.4)
Class	other class	reference level
	C00-D48	5.9 (1.2 – 30.0)

(1) Adjusted for significant variables of the univariate analysis of table IV.1. Variables in table IV.2 are those that remained in the multivariate analysis after a backward LR procedure.

➢ Internal validity final multivariate model

Table IV.3: Pseudo R^2 value of the final multivariate model (USA)

Step	-2 Log likelihood	Cox & Snell R Square	Nagelkerke R Square
1	68,489[a]	,243	,327
2	69,791[a]	,227	,305

Table IV.4: Overall percentage of correctly predicted values of the dependent variable (USA)

Observed			Predicted Dependent ,00	Predicted Dependent 1,00	Percentage Correct
Step 1	Dependent	,00	16	11	59,3
		1,00	7	29	80,6
		Overall Percentage			71,4
Step 2	Dependent	,00	10	17	37,0
		1,00	2	34	94,4
		Overall Percentage			69,8

APPENDIX V – DECISION SPONSORS OF FOMP'S (US SAMPLE)

The experimental (at least one FOMP) group of the US sample included 38 rare diseases (see appendix IV), which together obtained 225 OD's between January 2001 and April 2010 based on the Orphan Product Drug designation database of the FDA, as depicted in figure V.1 (please note that for opiate addiction no OD's were included due to the fact that only two first authorized OMP's were noticed. Both Subutex and Suboxone were authorized on the 8th of October 2002 by the FDA).

A further analysis of the 225 OD's revealed that the development of 11 (4.9 %) OD's was terminated before the approval of the first OMP for the same rare indication. As a result, 214 OD's remained in the US sample. From these 214 OD's, 178 (83.2 %) FOMP's were expected to be under development at or after the approval of the first OMP. Consequently, these 178 OD's were identified as FOMP. Furthermore, 35 (19.7 %) of these 178 FOMP's were authorized as FOMP for one of the 38 included rare diseases as of April 2010. From the remaining 36 (16.8 %) OD's it was, despite an in depth search in multiple sources, unknown whether they were under development at or after the market approval of the first OMP for the same rare disease. Nevertheless, from the data collection it was observed that all the sponsors of the 178 FOMP's decided to continue further development after the market approval of the first OMP for the same rare indication.

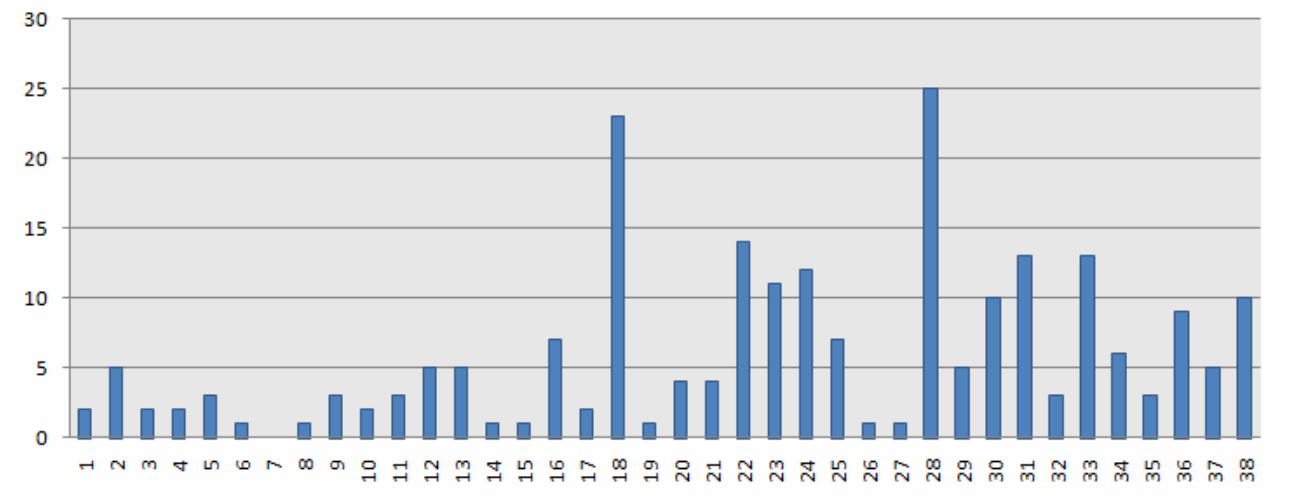

Figure V.1: OD's per rare indication in the experimental group (N = 225) (USA) (based on FDA, 2010a)

(1 = Fabry disease, 2 = Gaucher disease, 3 = Lennox-Gastaut syndrome, 4 = Mucopolysaccharidosis type I, 5 = Acromegaly, 6 = Short bowel syndrome, 7 = Opiate addiction, 8 = Giardiasis, 9 = Pompe disease, 10 = Von Willebrand's disease, 11 = Angioedema, 12 = Ulcerative colitis, 13 = Crohn's disease (pediatric patients), 14 = Cryopyrin-assisted periodic syndromes, 15 = Idiopathic hypereosinophilic syndrome, 16 = Squamous cell cancer of the head and neck, 17 = Chronic iron overload, 18 = Chronic lymphocytic leukemia, 19 = Replacement solution during continuous renal replacement therapy, 20 = Gastrointestinal stromal tumor, 21 = Malignant pleural mesothelioma, 22 = Chronic myeloid leukemia, 23 = Renal cell carcinoma, 24 = Pulmonary arterial hypertension, 25 = Juvenile idiopathic arthritis, 26 = B-cell non-Hodgkin's lymphoma, 27 = IGF-1 deficiency, 28 = Multiple myeloma, 29 = Malaria, 30 = Myelodysplastic syndromes, 31 = Acute lymphoblastic leukemia, 32 = Thyroid cancer, 33 = Hepatocellular carcinoma, 34 = Chronic immune thrombocytopenic purpura, 35 = Osteosarcoma, 36 = Huntington's disease, 37 = Cutaneous T-cell lymphoma, 38 = Glioblastoma/malignant glioma)